Title : Single Shot Liposomal Bupivacaine (EXPAREL®)/bupivacaine versus Continuous Erector Spinae Plane Block Catheter in Patients Undergoing Video Assisted Thoracoscopic (VAT) Surgery; Single Center Non Inferiority Open Label Prospective Randomized Clinical Trial

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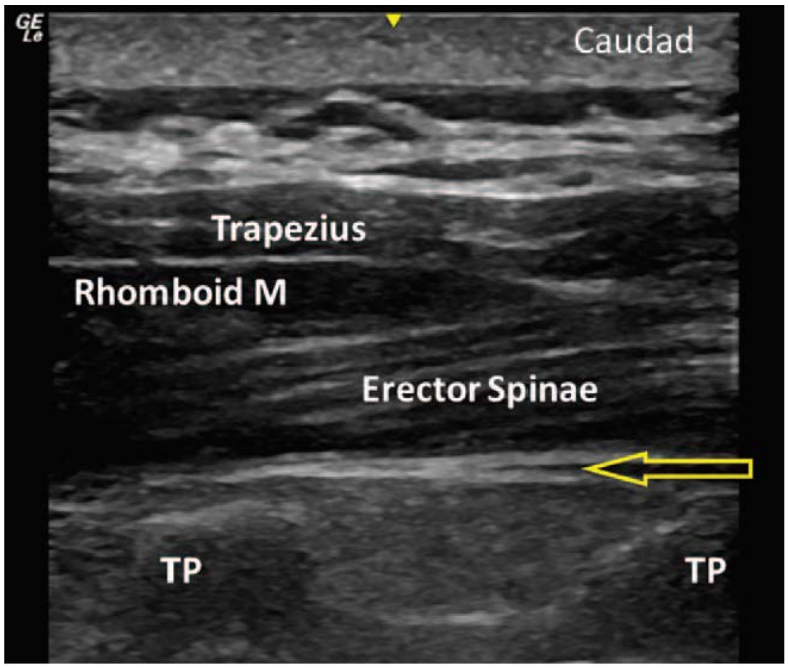
Background and Rationale

Roughly 51 million Americans undergo various inpatient surgeries with opioids being the mainstay of acute pain management.[1] Excessive opioid prescriptions for postoperative pain control have been related to the opioids-related crisis.[2,3] Preoperative opioid use, lower socioeconomic status, medical comorbidities and preexisting depression have been shown to cause chronic persistent opioid use after surgery.[4] Over 60% of people with opioid abuse obtain the medication from friends or relatives with unused prescriptions.[5] Thus, an effective acute pain management technique that mitigates opioid consumption for post-operative pain management warrants research.

In the perioperative period, a multidisciplinary approach that emphasizes various opioid sparing techniques can mitigate the risk of persistent chronic opioid use after surgery[6,7]. Anesthesiologists are the forefront players in providing effective pain control strategies in the perioperative period. Nerve blocks have been shown to effectively provide pre-emptive analgesia and acute post-operative pain relief, while preventing central sensitization and chronic neuropathic pain.[8]

Video assisted thoracoscopic (VAT) surgery has gained popularity among thoracic surgeons. This technique has been shown to be superior in improving post-operative lung function, decreasing hospital stays and has better patient satisfaction compared to traditional open thoracotomy.[9,10.] This minimally invasive technique has been widely used in various thoracic surgeries; lobectomy, wedge resection, decortication and pleurodesis. Some patients undergoing VAT surgery have been known to develop acute and chronic neuropathic pain.[11,12] The intercostal injury has been proposed as mechanism of chronic pain and numbness following VAT surgery.[13]

Although thoracic epidural was once considered a gold standard for acute pain management following thoracic surgery, this technique is becoming less popular in the VAT surgery.[14] While shown to be effective in acute post-surgical pain control, paravertebral block and intercostal block require an experienced operator, multiple level injections and risk of pneumothorax.[15] Recently, fascial plane block (erector spinae plane block, serratus anterior plane block, PEC, transverse thoracic plane block) have gained wide popularity in thoracic wall analgesia. Of interest is ultrasound guided Erector Spinae Plane (ESP) block, a novel technique first described in 2016 by Forero et al. (2016)[16]. The uniqueness of this technique is the minimal risk as compared to neuraxial blockade because of the myofascial location of this block. ESP block has been utilized for thoracic, cardiac, shoulder and abdominal surgeries with excellent pain control post operatively.[17-20] ESP blockade at the level of T5 spinous process provides analgesia from T2 to T10 sensory level.[21] The proposed mechanism of action of ESP block is due to diffusion into paravertebral space, effectively blocking the dorsal and ventral rami of the spinal nerves, as well as the rami communicantes that transmits sympathetic fibers as well as the intercostal nerves.[22-24]

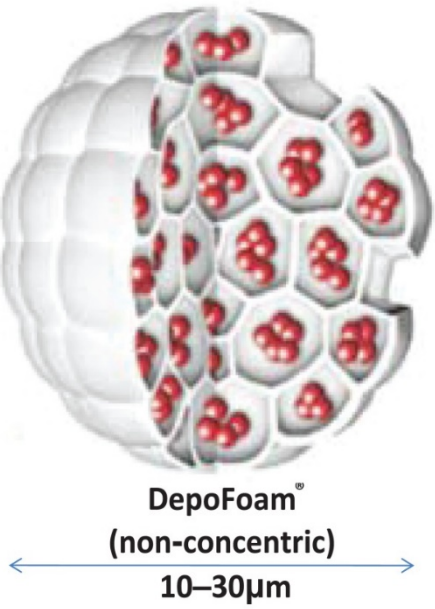


Reproduced from Forero, M., Rajarathinam, M., Adhikary, S., & Chin, KJ. (2017). Continuous Erector Spinae Plane Block for Rescue Analgesia in Thoracotomy After Epidural Failure: A Case Report, *A Prac*, 8(10), 254-256.

Figure 1. Showing ultrasound anatomy depicting the skin, subcutaneous tissue, trapezius muscle, rhomboid muscle, erector spinae muscle and the tip of the transverse processes. The arrow shows the erector spinae plane location for successful deposition of the local anesthetic.

The Food and Drug Administration (FDA) has approved liposomal bupivacaine for interscalene block, bunionectomy, hemorrhoidectomy, transversus abdominis plane block and wound infiltration. Liposomal bupivacaine, or EXPAREL® the brand name, is a long-acting extended release liposomal bupivacaine with microsomal liposomes (DepoFoam drug delivery system) containing multiple aqueous chambers of encapsulated bupivacaine. Bupivacaine is slowly released from the liposomes by diffusion as the unprotonated (uncharged) from of bupivacaine.

This preparation allows sustained release of bupivacaine at the site of injection without exposing patients to toxic plasma concentration. [25-26]



Reproduced from https://www.researchgate.net/figure/Cross-sectional-diagram-of-DepoFoam-containing-bupivacaine-Image-supplied-courtesy-of_fig2_232226382

Figure 2 Showing The DepoFoam system containing the bupivacaine.

This open label non inferiority prospective randomized clinical trial is important to confirm the hypothesis Single Shot Liposomal Bupivacaine (Exparel)/Bupivacaine in erector spinae plane block is non inferior compare to continuous erector spina plane block catheter group. The comparison of single shot ESP blockade using long acting local anesthetic with a continuous catheter technique is important to identify single shot ESP block using liposomal bupivacaine/bupivacaine as an acceptable method of pain relief. Currently, to the best of our knowledge, there is no prospective randomized clinical trial comparing Single Shot Liposomal

Bupivacaine (Exparel)/Bupivacaine in erector spinae plane block in patients undergoing VAT surgery.

Objectives

The purpose of this study is to evaluate erector spinae plane block using Single Shot Liposomal Bupivacaine **(EXPAREL®)** plus bupivacaine for pain relief in comparison to continuous erector spinae plane block catheter using ropivacaine local anesthetic in patients undergoing video assisted thoracoscopic surgery (VATS).

Trial Design

Non-Inferiority Prospective Open Label Randomized Clinical Trial. Double arm study comparing effectiveness of Single Shot Liposomal Bupivacaine **(EXPAREL®)** plus Bupivacaine (SS) and continuous erector spinae plane block catheter using ropivacaine intermittent automatic bolus (CC) in patients undergoing VAT surgery.

Study Setting

This trial will be done at Robert Packer Hospital in Sayre, PA. The Department of Anesthesiology will be conducting this research. The research will be conducted in the operating room (OR) and post-operative cardiothoracic surgical unit at Guthrie Robert Packer Hospital.

The erector spinae block will be done in the preoperative area, a fully monitored area with immediately available resuscitation and airway equipment. The VAT surgery will be done in the general operating room and, upon completion of the surgery, study subjects will be transferred to Prep and Recovery Unit (PRU) for immediate post-operative care. Data collection will occur in the operating room, PRU and the post-operative cardiothoracic surgical floor at Guthrie Robert

Packer Hospital. If the participant is discharged prior to 72 hours the surveys will be completed in their outpatient location.

Inclusion Criteria

Subjects who are age > 18, undergoing video thoracoscopic surgery, and following Guthrie Robert Packer Hospital's Enhanced Recovery After Surgery (ERAS) protocol for Thoracic Surgery will be included in this study.

Exclusion Criteria

The exclusion criteria is weight < 50 kg, pregnant subjects, left ventricular ejection fraction < 30%, history of drug or narcotic abuse, history of allergic to amide local anesthetic, presence of contraindication for erector spinae plane block (local skin infection, sepsis, severe coagulopathy) unable to provide consent, unable to use pain rating scales as demonstrated by verbal feedback, preoperative chronic pain on narcotics, history of renal insufficiency (Creatinine > 1.5 mg/dl), preoperative mild liver impairment (i.e. AST/ALT above 1.5 times the upper normal limit) and lactating women. Urine pregnancy test will be done on all female patients of childbearing age to exclude pregnancy unless there is a history of hysterectomy.

The following subjects will be withdrawn from study data analysis but will remain in the study for safety monitoring and study data collection as they have received the treatment: subjects that require conversion into open thoracotomy, and subjects who failed nerve block, defined by inability to determine the local anesthetic spread in the erector spinae plane on the ultrasound image. A screen failure is a participant who does not meet eligibility criteria after consenting or chooses to withdraw prior to surgery.

Consent

Written consent will be required for all study participants prior to participation and will be obtained by the principal investigator (PI) or a sub-investigator during the preoperative period.

Sample Size

A power analysis was carried out using the PASS software [27] to determine the appropriate sample size given power set at $1 - \beta = 0.90$. One-tailed alpha was set at the Bonferroni-adjusted level 0.008 given six time points at which the two treatment groups will be compared. The noninferiority limit was set as a between-group difference of two on the 11-point numeric pain scale, representing a clinically meaningful change. Assuming the standard deviation in each group is two, and that up to 20% of the sample may not complete the follow-up measures, the necessary sample size is 74 ($n = 37$ in each treatment group).

Study Endpoints

Primary Endpoint

Numerical Rated Pain Scale (NRP) while rest and with cough at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours and 48 to 72 hours post extubation. If the subject is discharged prior to 72 hours post-surgery, a telephone interview will be done to assess the post-operative numerical pain score.

Secondary Endpoints

Post-operative opioid consumption at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours, and 48-72 hours post VAT surgery. All opioids will be calculated to morphine equivalents to determine total morphine requirements for each interval. Cumulative morphine equivalents used at time 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours, and 48-72 hours will be

documented. If the subject is discharged prior to 72 hours post-surgery, a telephone interview will be done to assess the post-operative opioid consumption.

Total intraoperative opioid and adjunct pain medication (acetaminophen, gabapentin and ketorolac) consumed postoperatively at 0-4 hours, 4-8 hours 8-12 hours, 12-24 hours, 24-48 hour and 48-72 hours, post-operative incentive spirometry changes from preoperative baseline at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours and 48-72 hours, length of hospital stay, number of days ESP catheter in place, postoperative quality of recovery score (QOR-15), 24-48 hours (day 1) and 48-72 hours (day 2) post operatively and adverse events associated with erector spinae block and Single Shot Liposomal Bupivacaine (Exparel)/Bupivacaine.

Interventions

Participants will be screened for eligibility once decision has been made for thoracoscopic surgery. The cardio-thoracic surgery department will screen for potential recruitment. The study will be introduced by the surgeon and a consent document offered for review. After fulfilling the inclusion and exclusion criteria, consent will be obtained by the anesthesiologist sub investigator at the pre-admission appointment for the surgery. If the subjects need more time to review before deciding to participate, a consent form will be given for review before a decision is made at a later time.

At the time of consenting, baseline incentive spirometry will be done, baseline quality of recovery questionnaire (QOR-15) which consist of 15 questions related to five domains of patient reported health status (pain, physical comfort, physical independence, psychological support and emotional state) will be administered and the patient will be educated on how to use the pain assessment tool during the study, the 11-point Numerical Rated Pain Scale (NRP).

On the day of the surgery, the participant's history, physical, and laboratory results will be reviewed to confirm study eligibility by the study coordinator and the principal investigator/sub-investigators.

Randomization and Blinding

A computer-generated randomization table will be used for subject allocation to one of the two treatment arms; the Single Shot erector spinae using Liposomal Bupivacaine**(EXPAREL®)** plus Bupivacaine (SS) or erector spinae plane continuous catheter group (CC) using ropivacaine 0.2 % intermittent automatic bolus technique.

In the SS group, the study drug will be 10 mL of EXPAREL (133mg) mixed with 20 mL Bupivacaine HCL 0.25 % (50mg). A total volume of 30 cc will be injected into the erector spinae plane on the operative side at level of T5 transverse process.

In the CC group, the study drug to be used is 20-30 cc of bolus Ropivacaine 0.5 % into the erector spinae plane via catheter placement. Subsequent analgesia will be maintained by using electronic infusion pump (Sapphire ™ Multitherapy Pump; San Clemente, CA, USA) which will be programmed to deliver 20 cc intermittent Ropivacaine 0.2% automated bolus every 3 hours, with an additional patient demand bolus of 5 cc ropivacaine 0.2% with a lockout period of 30 min in the postoperative period at the PRU.

Blinding is not possible in this study because the CC group has an indwelling nerve catheter whereas the SS group does not.

The pharmacy department of the Robert Packer Hospital maintains the randomization table. The day prior to the planned surgery the instructions to randomize the participant is sent to the pharmacy. The anesthesiologist advances the treatment allocation orders for the study. The

pharmacist prepares the study medication on day of surgery. The randomization is sequential to the actual surgery date.

Procedures

Erector Spinae Plane (ESP) Block Method

Ultrasound guided ESP block will be performed by single experienced anesthesiologist in both groups of study subjects. In the preoperative block room, 5 lead continuous electrocardiogram, noninvasive cuff blood pressure and continuous pulse oximetry will be applied to the study subjects. A 20-gauge IV access will be obtained by preoperative nursing staff. Supplementary oxygen will be administered, and patients will be positioned in sitting position. An Immediate airway rescue cart will be stationed where the block will be performed together with Intralipid, which is a rescue drug in the event of local anesthetic toxicity.

After appropriate monitoring, a time out will be completed, identifying the correct patient and correct procedure. Midazolam 1-2 mg in titrating dose will be given for anxiolysis. The skin will be cleaned with antiseptic chlorhexidine prep. A high frequency 6-13 MHz linear array transducer (HFL38x, Sonosite Inc Bothell, WA) will be placed in longitudinal orientation 3 cm lateral to T5 spinous process.

For the SS group, a 21 gauge 100mm echogenic needle (SonoPlex II Facet; Pajunk, Geisingen, Germany) will be used and an 18G catheter over the needle set for the CC group (E Cath ; Pajunk, Geisingen, Germany). Using in plane technique, the echogenic needle will be directed from caudal to cranial direction. Under continuous visualization of the needle tip, contact will be made with T5 transverse process. Then 1-2 mL of sterile normal saline, will be injected to confirm lifting of the erector spinae muscle. After negative aspiration, this will be followed by injection of the study drug, in 5 mL increment with continuous visualization of the linear spread of the local anesthetic

and separation of the erector spinae fascia plane from the transverse process. In the event the needle tip cannot be adequately visualized, the procedure will be aborted. Positive block characterized by sonographic evidence of the local anesthetic spread with evidence of lifting of the erector spinae muscle plane.

Multimodal analgesia in ERAS protocol

Thoracic surgery multimodal analgesia as per ERAS protocol will be utilized in all subjects. Preoperatively, acetaminophen 1000mg orally, gabapentin, 300mg orally and celecoxib 200mg orally will be given on the preoperative holding area.

Postoperatively, acetaminophen 1000 mg Q8 hour prn, Gabapentin 100mg orally TID, Oxycodone 5 mg orally Q4H PRN for moderate pain, Oxycodone 10 mg orally Q6H PRN severe pain and morphine IV 2mg (moderate pain) and 4mg (severe) pain will be given for breakthrough pain 4 hourly as needed.

Anesthetic regimen

Intraoperative monitoring includes standard ASA monitor, Bispectral Index (BIS) and urine output. General anesthesia will be induced using propofol, fentanyl and rocuronium using balanced anesthetic technique. Maintenance of anesthesia will be achieved with inhalation agents, either sevoflurane, desflurane or isoflurane. For intraoperative analgesia, boluses of intravenous fentanyl only will be used for both groups.

Video Assisted Thoracic Surgery (VATS) Approach

The VATS procedure is done in a standard fashion. We utilize three ports, posterior 5mm camera, anterior inferior 5mm assistant, and 4cm working port in the 5th intercostal space. Dissection of the lung and lymph nodes proceeds from posterior to anterior with division of structures with bipolar electrocautery and endoscopic staplers. Extraction of the lung tissue is

done through the working port with an endocatch bag and a chest tube is placed through the anterior port.

Postoperative Care

On arrival in PRU, subjects will be attended by nursing staff and placed on monitors. Intravenous fentanyl or hydromorphone as needed will be given based on the numerical rated pain ratings. Chest x ray will be taken and reviewed in the PRU. Signs and symptoms of local anesthetic toxicity (LAST) will be screened in the PRU.

The ESP catheter in the CC study group will be connected to electronic infusion pumps in the PRU. (Sapphire ^{TM} Multitherapy Pump; San Clemente, CA, USA) which will be programmed to deliver automatic intermittent bolus of 20 cc of ropivacaine 0.2% every 3 hours. Patient controlled bolus of 5 cc of ropivacaine 0.2% will be allowed at a lockout period of every 30 minutes.

All study subjects will be admitted and observed in the cardiothoracic surgery floor at least for 24 hours post VATS with telemetry monitoring. In addition to standard resuscitation medication and equipment, Intralipid will be made available while the study subjects remain on the post-operative floor in the event local anesthetic systemic toxicity suspected. Signs and symptoms of LAST will be screened by nursing staff. If the study subject experiences any signs and symptoms of LAST, 12 leads EKG, vital signs, and plasma levels of bupivacaine or ropivacaine will be sent immediately. In addition to that, after the blood draw, prophylactic treatment of presumed LAST toxicity with Intralipid infusion 1.5cc/Kg will be done. Additional use of bupivacaine as local anesthetic will be avoided for 96 hours on subjects receiving single shot liposomal bupivacaine (SS) group; this will be accomplished through provider and patient education as well as a patient wrist band worn by patients who receive Exparel injection. If this occurs the patient will be monitored and assessed for any adverse events.

If the study subjects are deemed suitable for discharge home in less than 72 hours, the continuous catheter in the CC group will be removed. Subjects will be screened for LAST signs and symptoms for 8 hours after removal of the catheter and before being sent home. Subjects will be educated on signs and symptoms of LAST (metallic taste, ringing in the ears, perioral tingling, agitation, seizure and cardiac arrythmias) and if these signs are present, subjects will be instructed to go to the nearest emergency department for medical evaluation.

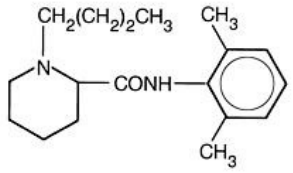
Following home discharge, a telephone call will be made by the investigator team every 24 hours until 72 hours post-operative period to collect data on opioid consumption, QOR-15 questionnaire, numerical pain score, and screening questions for signs and symptoms of LAST.

Investigational Product

EXPAREL® (bupivacaine liposome injectable suspension), a marketed product indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

EXPAREL® (bupivacaine liposome injectable suspension) is a white to off-white, milky aqueous suspension diluted with preservative-free normal (0.9%) saline for injection or lactated Ringer's solution within 4 hours of preparation in a syringe.

Chemically, Bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine has the following structural formula:



EXPAREL® (bupivacaine liposome injectable suspension) is available as 266 mg/20 mL (13.3 mg/mL) single-dose vial or 133 mg/10 mL (13.3 mg/mL) single-dose vial.

The general objectives of this proposed investigation are to establish the incidence of adverse events in patients receiving a Single Shot Liposomal Bupivacaine (Exparel)/Bupivacaine, and to assess the efficacy of the erector spinae nerve block using Single Shot Liposomal Bupivacaine (Exparel)/Bupivacaine in order to determine if this is a safe regimen for routine use in patients undergoing video-assisted thoracic surgery (VATS).

EXPAREL® (bupivacaine liposome injectable suspension) is an FDA-approved prescription drug that will be administered at a dose in accordance with the package insert but the site of the injection will be investigational. We plan to use a 10 mL vial (133 mg) of EXPAREL® mixed with 20 mL Bupivacaine HCL 0.25% (50 mg) for the SS group. A total volume of 30 cc will be injected. The ratio of the milligram dose of the bupivacaine and liposomal bupivacaine in the mixture is less than 1:2 as per package insert.

Potential Risks

The package insert for EXPAREL® (bupivacaine liposome injectable suspension) describes potential risks for patients:

Central Nervous System Reactions

The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also dependent upon the particular

drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesia, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions

Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed, and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Allergic Reactions

Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members

of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

Accidental Intravascular Injection

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Adverse Reactions

Table 1. Adverse reactions reported with use of Exparel

Incidence	**Adverse reactions**
Most common (≥ 10%)	Nausea, constipation, vomiting
Common (≥2 or ≤ 10%)	Pyrexia, dizziness, peripheral edema, anemia, hypotension, pruritus, tachycardia, headache, insomnia, postoperative anemia, muscle spasm, hemorrhagic anemia, back pain, somnolence, procedural pain
Less common/rare (<2%)	Chills, erythema, bradycardia, palpitations, supraventricular/ventricular extrasystoles, ventricular tachycardia, anxiety, urinary retention, pain, edema, tremor, postural dizziness, paresthesia, syncope, incision site edema, procedural hypertension/hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, sinus bradycardia, hypertension, pallor, laryngospasm, respiratory depression, respiratory failure, body temperature increased, BP increased, BP decreased, oxygen saturation decreased cold sweat, urticaria, confusional state, depression, agitation, hyperhidrosis, restlessness, blurred vision, tinnitus, hypoxia, apnea, urinary incontinence, drug hypersensitivity, hypersensitivity

Reproduced from Exparel Prescribing Information. 23 Jan 2012. Pacira Pharms, Inc. San Diego, CA

Risk Mitigation

To minimize risks, all study participants will receive the injection being studied at the Robert Packer Hospital, which has full resuscitation facilities available. There will be a presence of one anesthesiologist or certified registered nurse anesthetist (CRNA) directly monitoring the study subject from the time of injection to the arrival of the patient in the PRU.

Any interventions necessary to treat adverse events will be given at the discretion of the attending physician and consent to do so will be provided by the patient. EKG will be monitored continuously from the time of injection to the discharge of the patient. Upon transfer from PRU, patients will be on the telemetry floor. The availability of emulsified lipid or Intralipid will be made available immediately in the operating room and PRU. Signs and symptoms of LAST will be screened continuously by the nursing team, investigator team and surgical team.

Outcomes & Definitions

Primary Endpoint

"NRP (Numerical Rated Pain Score) at 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery" is defined as numerical pain score with 0 being no pain and 10 being the most severe pain. The value obtained within the specified time interval will be used for analysis. The highest NRP value will be taken if multiple values are obtained within specified time interval.

Secondary Endpoints

"Post-operative opioid consumption at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery" is defined as time that starts from the arrival to PRU and opioid that was administered to achieve adequate pain control at the specified time interval.

All opioids will be converted to morphine equivalents in order to calculate total morphine requirements for each interval. Cumulative morphine equivalents used at time interval at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery will be done.

"Total intraoperative narcotic" is defined as total opioids administered in the operating room.

"Adjunct pain medication consumption at 0-4 hours, 4-8 hours 8-12 hours, 12-24 hours, 24-48 hour and 48-72 hours postoperatively" is defined as all non-narcotic pain medications such as acetaminophen, gabapentin, ketorolac, etc.

"Incentive spirometry changes at rest and with cough post extubation at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery" is defined as the percentage change from preop incentive spirometry value at 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (day 2), 48-72 hours (day 3) post VAT surgery . The value obtained within the specified time limit will be used for analysis, and average spirometry value will be used if multiple values are obtained within each specified time interval.

"Length of hospital stay" is defined in days.

"QOR-15" is a survey on patient reported outcome which consists of 15 questions related to quality of recovery. It will be administered at the time of consenting (baseline), and repeated on days 1, 2 and 3 post VATS surgery.

Adverse events associated with liposomal bupivacaine and erector spinae block will be recorded as listed in table 2. Common Terminology Criteria for Adverse Events (CTCAE) version 5, published November 27, 2017, will be used for standard classification of adverse events for this project. Additionally, will record any of the following:

- Cardiac: anginal, myocardial infarction, arrythmia suspect related to local anesthetic
- Neurologic: Transient Ischemic attack (TIA), stroke, seizure, nerve injury from ESP block
- Gastrointestinal: Nausea, vomiting, constipation, ileus, bowel obstruction
- Pulmonary: pneumonia, pneumothorax
- Infection at the site of the block
- Local anesthetic systemic toxicity (LAST) necessitating use of Intralipid

Benefits

There may be no benefit to participants in this project. The hope is to attain longer acting pain control, which may result in quicker recovery, shorter hospital stays, better breathing techniques due to pain relief, and less use of narcotics which may decrease risks of nausea, vomiting and constipation. This information may lead to knowledge that could be useful in decision-making for local pain relief in future patients.

Data Collection and Management

Upon completion of the overall intervention, data will be downloaded from the EPIC electronic health record with the help of EPIC consultants from the database by an analyst not involved in the research. Telephone conversations will be done to assess pain score and opioid consumption if the subject is discharged home during the data collection time period (72 hours post intervention).

Data will be stored for five years after the conclusion of the trial in a secure location and access will be allowed to investigators. In compliance with the ICH/GCP guidelines, the investigator will maintain all source documents that support the data collected from each subject, as well as all study documents.

Data Safety Monitoring

A Data Safety Monitor (DSM) will be appointed to monitor and identify alarming trends in adverse events involving the study subjects. The DSM will not be involved in data collection or patient interaction. The DSM will be unblinded to assist in detecting trends of serious events that may warrant modification or stopping the study. The DSM will conduct periodic review on every 5 patients enrolled in the study. If enrollment is slow, then the DSM will review at least annually.

A Clinical Monitor will be appointed to review all adverse events in each study subject. This will also ensure that the adverse events occur with reasonable expectation within the study. The Clinical Monitor will contact the DSM within 24 hours of recognizing the occurrence of adverse events or serious adverse events. The DSM will review the events in unblinded fashion and if there is an alarming trend significant enough to modify or suspending the trial, then the DSM will notify the PI.

The study will be stopped if one death where a clear alternate cause is not readily apparent, two non-fatal serious adverse events where a clear alternate cause is not readily apparent and two moderate to severe symptoms related to local anesthetic systemic toxicity.

Statistical Methods

Demographic and clinical characteristics of the study groups will be reported by obtaining number of observations (percentages) and mean (standard deviation) or median (range) as required for the primary and secondary outcomes. Comparison of treatment groups will be performed by using ANOVA with planned contrasts between the groups at each time point. A Bonferroni adjustment will be made for multiple comparisons in the post hoc testing. Test statistics, P-values and 95% CI (Confidence Interval) will be obtained to report any statistically significant differences.

Research Ethics Approval

This research protocol will be submitted for approval to the Institutional Review Board of the Guthrie Clinic prior to its implementation.

Funding

Grant from Donald Guthrie Foundation for Education and Research is supporting this project.

Confidentiality

The minimal amount of Protected Health Information (PHI) necessary to identify patients (medical record number and date of birth) will be collected and stored in a secure, password-protected file on a Guthrie workstation. This information will be kept for the duration of the trial to allow for collection of information from the subject's electronic medical record as described under "Data Collection and Management." All information will be de-identified at the conclusion of the trial.

Declaration of Interest

Poovendran Saththasivam MD, Sudhakar Kinthala MD, Burdett Porter MD, and Mary Hicks, RN-NPD have no conflicts of interest to report.

Environmental Assessment of Human Drug and Biologics Applications

An Environmental Assessment is not required because the action requested qualifies for a categorical exclusion per 21 CFR 25.31(e). To the applicant's knowledge, no extraordinary circumstances exist per 21 CFR 25.15(d)

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