



PROTOCOL

Title: A Pilot Study: A Comparison of Liposomal Bupivacaine (“Exparel™”) to Bupivacaine HCl in Transversus Abdominis Planus (“TAP”) Block for Abdominal Gynecologic Surgery

Sponsor: Mark Shahin, MD,
Abington Memorial Hospital, 1 Widener
Hanjani Institute for Gynecologic Oncology
215-885-0220

Principal Investigator: Heidi Ching, MD
Abington Memorial Hospital
1200 Old York Road Price MOB Suite 109
215-481-4211
518-813-0526

The following persons are sub-investigators for this research study:

Jacqueline Kohl, MD
Faith Pullinger, MD
Mitchell Edelson, MD
Elizabeth Burton, MD
Joel Sorosky, MD

I. Objectives/Purpose

The proposed pilot study is evaluating the use of Exparel™ in an anesthesia protocol for patients undergoing major lower abdominal gynecologic surgery. Exparel™ is a formulation of liposomal bupivacaine that is reputed to have a much longer duration of action compared to bupivacaine. Exparel™ has been originally demonstrated to be safe and effective in bunionectomy and hemorrhoidectomy. It has recently gained FDA approval for all surgical site infiltration including TAP (Transversus Abdominis Planus block) blocks. Exparel™ has also been studied in other procedures and demonstrated reduction in opioid use and median length of stay (LOS).

Currently, patients on the gynecologic oncology service undergoing major abdominal surgery are receiving a type of regional anesthesia using bupivacaine HCl known as a TAP block as part of an effort to decrease narcotic use post-operatively and decrease hospital length of stay. Bupivacaine has a known eight to twelve hour duration of action, thus addressing immediate post operative pain. As Exparel™ is anticipated to have a longer duration of action, the purpose of this study is to determine if TAP blocks with Exparel™ have an advantage over standard TAP blocks with bupivacaine HCl in reducing length of hospital stay in a randomized controlled trial. Our hypothesis is that TAP blocks with Exparel™ will result in reduced length of stay contributing to significant hospital cost savings. Secondary outcomes include total narcotic use (hypothesized to be reduced) and overall complication rates (hypothesized to remain unchanged). Given there are no published data on the efficacy and safety of using Exparel™ in open gynecologic abdominal surgery, this will be a pilot study.

II. Background Information:

Overview of Clinical Studies

Comparative efficacy and safety of liposome bupivacaine versus bupivacaine HCl has been analysed in order to reduce opioid burden in the post surgical setting. Specific procedures such as inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation, or bunionectomy, have been included in recent studies. In one of the pooled analysis, liposomal bupivacaine has been shown to reduce pain scores at a statistically significant level. Patients receiving liposomal bupivacaine were also less likely to experience opioid related adverse events.

The following safety information is derived from Exparel™'s website including prescribing information and important safety information. Exparel™ is indicated for single-dose administration into the surgical site to produce post surgical analgesia. In clinical trials, the most common adverse reactions following Exparel™ administration were nausea, constipation and vomiting. Other common adverse reactions include pyrexia, dizziness, anemia, hypotension, prurities (incidence between 2% and 10%). The rare adverse reactions (incidence less than 2%) include, but are not limited to, chills, erythema, bradycardia, pain, edema, syncope.

Exparel™ has been demonstrated to be safe and effective for procedures such as hemorrhoidectomy and bunionectomy, as well as for surgical site infiltration such as TAP blocks. Exparel™ use in open abdominal gynecologic surgery for TAP block has not yet been studied specifically. Monitoring of cardiovascular and neurological status, as well as vital signs, should be performed before, during and after administration of Exparel.

III. Procedures

Patients undergoing laparotomy will be randomized to either Exparel™ or bupivacaine HCl. Randomization will occur through computer generated random assignment. Given the nature of the medication itself, bupivacaine and Exparel™ have physical inherent differences after manufacture and the anesthesiologist will not be able to be blinded. Patients will be blinded to the type of TAP block they receive.

A. Inclusion and Exclusion of Subjects

Inclusion criteria

1. TAP blocks placed after the laparotomy incision is closed, but before the patient is awake, and placed under ultrasound guidance with correct identification of the correct abdominal plane.
2. Consent for TAP block signed by patients preoperatively by anesthesiology

Exclusion criteria

1. All pregnant patients
2. All patients under 18 years of age
3. minimally invasive surgery such as laparoscopy or robotic assisted laparoscopy
4. medical contraindications to use of bupivacaine or liposomal bupivacaine such as severe hepatic and/or renal disease

We hope to include 128 subjects in this study in order to reach statistical significance. Please see Appendix 1 for sample size calculations.

B. Assessment of Efficacy/Measurement

Efficacy will be measured through comparing length of hospital stay, total narcotic use, and complications/adverse effects such as nausea, vomiting, constipation and pruritis.

C. Treatment of Subjects

Subjects will need to provide consent for both the surgery and TAP block provided by an anesthesiologist. Post operatively, narcotic availability will not be withheld.

D. Validity

Internal validity will be addressed by randomizing the subjects to avoid selection bias. Patients will also be blinded to the type of TAP block they will receive to eliminate recall bias.

E. Discontinuation of the Study

Study involvement will be discontinued if the subject displays an immediate reaction to the local anesthetic, whether bupivacaine or liposomal bupivacaine. Interim analysis after enrollment of first 50 patients will be done and if there is a clear benefit of use of Exparel™ over Bupivacaine, the study will be discontinued.

IV. Methods

1. Informed consent will be offered to patients in pre op area and patients will be randomized. Charts will be labeled with a card stating bupivacaine, vs Exparel. A consent for anesthesia including TAP block is signed by patients preoperatively.
2. All TAPs will be placed after the laparotomy incision is closed but before the patient is awake.
3. Anesthesia will place the TAP with Ultrasound.
4. We will typically not open the Exparel before closure of fascia. Once EXPAREL is open it is only good for 4 hours so should NOT be opened until right before you are ready to use
5. Surgeon will notify anesthesia if the incision is extended above the umbilicus
6. When performing a bilateral TAP with Exparel and the incision is below the umbilicus: the 20 ml vial of Exparel, containing 266 mg, will be diluted with 20 ml of 0.25% bupivacaine (containing 50 mg of bupivacaine) and 20 ml saline (60 ml total). That total volume will be divided into two 30 ml syringes, and each will be used (per side) for the TAP blocks.
7. When performing a bilateral TAP with Exparel and the incision extends above the umbilicus: 160 ml of saline will be mixed with 20 ml (266 mg) of Exparel for a total volume of 80 ml. Of this volume, 40 ml will be passed off to the surgeon for direct infiltration into the supraumbilical portion of the incision. The remaining volume (40 ml) will be retained by the anesthesia team. That remaining volume will be subdivided into two syringes, and to each syringe will also be added 10 ml of 0.25% bupivacaine (25 mg), for a total volume per side of 30 ml, which will be used in the TAP blocks.

8. When performing a bilateral TAP with Bupivacaine 0.25% and the incision is below the umbilicus: 30 ml of 0.25% bupivacaine is drawn up and given on each side after identification of planes by the anesthesiologist (need 2 vials).
9. When performing a bilateral TAP with Bupivacaine 0.25% and the incision extends above the umbilicus: 30 ml of 0.25% bupivacaine is drawn up and given on each side after identification of planes by the anesthesiologist (need 2 vials). A 3rd vial of 30 ml 0.25% bupivacaine will be drawn up and is directly infiltrated into the surgical site (above and below the fascia prior to closure of fascia) extending above the umbilicus by the surgeon.
10. Anesthesia will identify the correct abdominal plane with ultrasound. Normal saline 1-5 ml will be used initially, for hydrodissection, to provide confirmation of needle tip position. Once confirmed, 5ml per side of 0.25% bupivacaine will be injected into the plane with Exparel to follow. This will allow some short term activity of TAP block before Exparel starts to take effect. In addition, at the recommendation of the anesthesia, patients in both Exparel and plain bupivacaine groups will be given hydromorphone 0.5 mg IV coincident with the performance of the TAP block, prior to emergence from anesthesia and extubation.
11. Our goal is to collect information on total opioid usage, length of stay, as well as complications/adverse effects.

V. Statistics

Results from the study will be submitted to the department's statistician for statistical analysis. Interim analysis may be performed to assess the efficacy of Exparel™.

VI. Quality Control and Assurance

Every anesthesiologist that will be administering the TAP block in this study will perform the TAP block in a controlled fashion under certain guidelines whether using bupivacaine or Exparel™. Every surgeon that is participating as a sub-investigator will be informed of the correct procedure and protocol.

VII. Ethics

There has been much data showing that TAP block is successful and reduces post operative pain using bupivacaine. The unknown effect of Exparel™ in TAP block for gynecologic surgery, especially in exploratory laparotomy, is the reason for the study. Exparel™ is much more costly than bupivacaine. If the use of Exparel™ results in significant reduction in length of stay, then expenditure for this agent is justifiable. Given that Exparel™ has been used in other types of surgeries for post operative pain relief, it is ethical to use Exparel™ in this type of study. Exparel™'s adverse effect profile, which includes nausea, vomiting and pruritis, is acceptable and therefore ethical to use in this study.

VIII. Data handling and Record keeping

- 1) review of charts - resident and attending notes
- 2) review of medication administration
- 3) two independent reviewers of charts

IX. Project Timetable/Flowchart

- 1) February 2016- IRB Submission - Consent/Protocol

- 2) March 2016 - IRB Resubmission
- 3) June 2016 - IRB Resubmission
- 3) July 2017 - February 2017 data gathering (8 months)
- 4) March 2017 - data analysis

References

- Baxter Richard, Bramlett Kenneth, Onel Erol, Daniels Stephen. Impact of Local Administration of liposome bupivacaine for post surgical analgesia on wound healing: a review of data from ten prospective, controlled clinical trials. *Clinical Therapeutics* 2013. 35 (3): 312-20.
- Bergese Sergio D, Ramamoorthy Sonia, Patou Gary, Bramlett Kenneth et al. Efficacy profile of liposomal bupivacaine, a novel formulation of bupivacaine for post surgical analgesia. *Journal of Pain Research* 2012;5 107-116
- Dasta Joseph, Ramamoorthy Sonia, Patou Gary, Sinatra Raymond. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the post surgical setting. *Current Medical Research & Opinion* 2012. 28 (10): 1609-15.
- Feierman Dennis E, Kronenfeld Mark, Gupta Piyush M, Younger Natalie, Logvinskiy Eduard. Liposomal bupivacaine infiltration into the transversus abdominis plane for post surgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients. *Journal of Pain Research* 2014: 7; 477-82.
- Haas Eric, Onel Erol, Miller Howard, Ragupathi Madhu, White Paul. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. *Am Surg.* 2012 May;78(5):574-81.
- Hutchins Jacob, Delaney Daniel, Isaksson Vogel Rachel, Ghebre Rahel G. et al. Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: A prospective randomized controlled study. *Gyn Onc* 138 (2015): 609-613.
- Hu Dee Dee, Onel Erol, Singla Neil, Kramer William, Hadzic Admir. Pharmacokinetic Profile of Liposomal Bupivacaine injection following a single administration at surgical site. *Clinical Drug Investigation* 2013. 33: 109-15.
- Sternlicht Andrew, Shapiro Max, Robelen Gary, Vellayappan Usha, Tuerk Ingolf A. Infiltration of liposome bupivacaine into the transverses abdominis plane for post surgical analgesia in robotic laparoscopic prostatectomy: a pilot study. *Local and Regional Anesthesia* 2014; 7:69-74.
- Viscusi Eugene, Sinatra Raymond, Onel Erol, Ramamoorthy Sonia. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain.* 2014 Feb; 30(2):102-10.