A Prospective Randomized Clinical Trial Comparing the Transversus Abdominis Plane Block versus Epidural Anesthesia for Enhanced Recovery Pathway Perioperative Management of Pain in Elective Colorectal Surgery

NCT # 02591407

December 9, 2015

TABLE OF CONTENTS

Protocol Summary	
Full Title	A Prospective Randomized Clinical Trial Comparing the Transversus Abdominis Plane Block versus Epidural Anesthesia For Enhanced Recovery Pathway Perioperative Management of Pain in Elective Colorectal Surgery
Short Title	TAP
IND Sponsor (if applicable)	St. Joseph Mercy Hospital Research Committee
Principal Investigator	Robert K Cleary, MD
Sample Size	176
Study Population	The study population will be composed of patient's ≥ 18 years of age undergoing elective colon and rectal surgery for colorectal neoplasia, diverticulitis, and other diseases of the colon and rectum.
Accrual Period	Nov. 2015 – Feb. 2017
Study Design	Randomized trial comparing transversus abdominis plane block to epidural anesthesia for the management of perioperative pain in elective colorectal surgery
Study Duration	Nov. 2015 – Feb. 2018
Primary Objective	The primary outcome for this study is the Numeric Pain Score (NPS) for elective patients undergoing elective colorectal surgery in the Enhanced Recovery Pathway (ERP) program.
Risks/Benefits	The risks of this study are the same as those for patients receiving TAP blocks and epidural catheters outside of the study as well as the standard risks of colorectal surgery. TAP blocks and epidural analgesia are currently standard of care and widely employed at SJMH.

KEY ROLES

Institution: St Joseph Mercy Hospital
Address: 5301 East Huron River Drive
Ann Arbor, MI 48104
Contact Person: Robert K Cleary MD
Phone Number: 734-358-9730
Fax Number: 734-712-8151
E-mail: Robert.Cleary@stjoeshealth.org

Sponsor: SJMH Research Committee

Individuals: Principal Investigator:

Robert .K Cleary MD, Director Colon and Rectal Surgery ERI
Institution: St Joseph Mercy Hospital
Address: 5325 Elliott Dr. Suite 104
Ypsilanti, MI 48197
Phone Number: 734-358-9730
Fax Number: 734-712-8151
E-mail: Robert.Cleary@stjoeshealth.org

Sub-investigators:

Daniel Felling, MD
Surgical Resident
St. Joseph Mercy Hospital

Cheryl Genord, R.Ph
Pharmacist
St Joseph Mercy Hospital

1. BACKGROUND INFORMATION

Adequate peri-operative analgesia is a vital component of post-operative management for patients undergoing colon and rectal surgery, affecting hospital length of stay, quality of life, and patient outcomes. There are many options for the peri-operative management of pain after elective colorectal surgery.[1] Randomized controlled trials have demonstrated improved perioperative pain management with epidural analgesia in postoperative colorectal patients when compared to intravenous and oral narcotic pain medications and are currently an integral component of Enhanced Recovery Pathway (ERP) programs. The benefit is believed to result from a decrease in the sympathetic overdrive that is associated with severe pain and surgical injury leading to decreased rates of ileus and fewer respiratory complications.[2] Epidural anesthesia is characterized by placing an epidural catheter into the epidural space at or below the level of the iliac crest (distal to the end of the spinal cord) prior to surgery. This catheter is secured to the patient's back and continuous analgesia (often bupivacaine) is administered from a pump. Risks of epidural analgesia are uncommon and include infection, bleeding, hypotension and bradycardia, urinary retention, and rarely temporary or permanent neurologic deficits.[4]

Other options for perioperative pain management include abdominal wall catheters placed either in the preperitoneal space at the time of surgery (OnQ®) or in the plane between the abdominal wall internal oblique and transversus abdominis muscles (TAP Block). A randomized controlled trial at this institution comparing epidural analgesia with the preperitoneal wound catheter pump (OnQ®) demonstrated that continuous epidural analgesia with bupivicaine provided better pain control on the day of surgery and on postoperative day one when compared to bupivicaine administered by the continuous preperitoneal pump.[5]

More recently, TAP Blocks that deliver bupivicaine in the plane between the internal oblique and transversus abdominis muscles have become popular in perioperative pain management for patients undergoing major abdominal open and minimally invasive surgery.[6-7] The ease of insertion and advantage of a single injection without the need for an indwelling catheter make this option ideally suited for elective colorectal surgery patients. The disadvantage to this modality is the short duration of action. Peak levels for epidural and abdominal wall peripheral nerve block occur at 30-45 minutes with subsequent decrease to insignificant levels in 3 to 6 hours.

Bupivacaine is a local anesthetic drug belonging to the amino amide group. Bupivacaine is indicated for local anesthesia including infiltration, nerve block, epidural, and intrathecal anesthesia. Exparel® is a long acting bupivicaine local anesthetic FDA-approved for single dose infiltration for post-surgical analgesia. It is bupivicaine in a liposomal suspension that significantly increases the duration of action. The bupivicaine in this product is attached to a proven product delivery platform, DepoFoam®. A single intraoperative abdominal wall injection treats pain at the source with reduced opioid requirements for up to 72 hours, considerably longer than standard bupivicaine. When used as part of a multimodal treatment ERP regimen, Exparel® can provide non-opioid pain control that lasts as long as the most intense postsurgical pain, without the need for catheters, pumps, or other delivery devices.[3] Exparel® has been shown to provide effective postsurgical analgesia when used in TAP Blocks.[8]

Because the duration of bupivicaine without liposomal suspension is short, there may be an advantage to using a long acting derivative such as Exparel® for TAP Blocks, especially with respect to decreasing narcotic pain medication needs after the first postoperative day.

This study compares two well-established treatment options within the context of a colon and rectal surgery ERP. Though both of these pain management options are utilized on a daily basis and considered standard of care in colorectal surgery, these two important pain treatment options have not yet been compared in a randomized controlled prospective trial. Epidural catheters are widely used for elective colon and rectal surgery and have the rare risk of central nervous system infections. If TAP Blocks are shown to be as effective as epidural analgesia in a randomized controlled study, this may result in a significant change in pain management for this patient population with the decreased associated risk. A significantly larger group of patients will likely receive Exparel® TAP Blocks rather than epidural catheters with the associated decrease in risk. Exparel® TAP Block would also be a reasonable option for those who are not candidates for epidural catheters (spinal stenosis, spinal fusion, patient refusal).

The outcome of this study will be considered meritorious scholarly activity and will be published in a peer-review journal. It will serve as a template for other surgical pain management programs at other institutions.

Pain Management in the field of colon and rectal surgery is rapidly changing and is undergoing constant re-evaluation. New information from this study will add considerably to the advancement of pain management programs in this field.

2. STUDY OBJECTIVE

The primary outcome is this study is the well-established Numeric Pain Score (NPS). A secondary outcome is the Overall Benefit of Analgesic Score (OBAS). This score was developed and validated by Lehman, et. al in 2010.[9] OBAS is a comprehensive pain score that includes the variables of vomiting, dizziness, and sweating (Appendix 1).

Other secondary outcomes include perioperative narcotic requirements measured in morphine equivalents, hospital length of stay, time to first flatus, time to first bowel movement, and institutional costs of TAP and epidural interventions.

3. STUDY DESIGN

This is a physician-generated single-center randomized trial comparing TAP block to epidural analgesia for the perioperative management of pain in elective open and minimally invasive (laparoscopic and robotic) colorectal surgery.

4. STUDY POPULATION

Inclusion Criteria

- Patients undergoing elective open and minimally invasive (laparoscopic and robotic) colon and rectal surgery for colorectal neoplasia, diverticulitis, and other diseases of the colon and rectum;

- Surgical procedure either through standard open or minimal invasive approach (laparoscopic or robotic);
- Patients ≥ 18 years of age;
- Able to provide informed written consent
- Patients capable of completing questionnaires at the time of consent

Exclusion Criteria

- Documented allergic reaction to morphine, hydromorphone, lidocaine, bupivicaine and/or fentanyl;
- Contra-indication to placement of epidural catheter (spinal stenosis, spinal fusion, elevated INR, anticoagulation, patient refusal, etc) or TAP block (patient refusal);
- Urgent or emergent surgery precluding epidural catheter placement or TAP block;
- Systemic Infection contraindicating epidural catheter placement or TAP block;
- Unwillingness to participate in follow up assessments;
- Prisoners
- Pregnant women

5. PATIENT RECRUITMENT & CONSENT

Due to the nature of this study; participants, nursing staff and the research team will not be blinded to randomization method. Standard analgesic options will be discussed with patients by the surgeons along with operative options, risks, and benefits, prior to scheduling operative intervention and per routine. The well-established Enhanced Recovery Pathway Program (ERP)

consists of patients with diseases of the colon and rectum seen in the surgeons clinic and inpatients on the Patient Care Unit. The ERP Nurse Navigator will review patient's records to determine which patients meet inclusion/exclusion criteria and are eligible to participate in the study. During the current pre-operative education classes, within ERAS, the Nurse Navigator will approach eligible patients and discuss the study. If the patient is interested, they will be given the opportunity to read the informed consent and ask questions regarding the study. Should they be willing to participate, the Nurse Navigator will obtain informed consent. Patients may also be consented in the surgeon's clinic by a research coordinator or investigator.

Informed consent and patient logs will be stored in the academic research department.

6. STUDY SCHEDULE

Patients will be asked their NPS and OBAS following consent during pre-operative education (baseline). NPS will then be obtained on operative day (0) and post-operative days 1, 2, and 3 from the electronic medical records that are documented by the patient care technicians every 8 hours. The OBAS will be collected by trained residents and nursing staff once a day on operative day (0) within 6 hours of recovery and between 0600 and 1200 on post-operative days 1, 2 and 3. If the patient is consented in the investigators office, pre-operative NPS and OBAS will occur there.

7. RANDOMIZATION

Two hundred patients will be randomized in blocks of ten with a 1:1 ratio. Standard open and minimally invasive (laparoscopic and robotic) approaches will have separate blocks. Patients

will be randomized using a web-based system called CREDIT. CREDIT maintains a patient log that includes randomization placement.

Randomization schedules were created using R (version 3.2.1), using 10 blocks were each selected has a 50% chance of being selected. The randomization process was conducted using box-muller to assign random numbers which was used to identify the selected treatment for each patient.

8. DATA COLLECTION AND MANAGEMENT

Demographic, health, and hospital stay data will be obtained from the Quality Institute. Data that is unavailable through electronic queries will be collected from the electronic medical record by a study team member. A pharmacist will collect PCA pain medication data that cannot be obtained from an electronic query of Pharmacy databases. All data will be entered into REDCap by a research study team member. Data will be stored in a locked office and password protected computer. Only members of the study team will have access to patient identifiers. Identifiers will be removed prior to analysis. All identifiers will be stored by the research coordinator in a secure location. Identifiers will be destroyed seven years following the conclusion of this study. (Data collection sheets, including adverse events Appendix 2).

9. RISKS AND BENEFITS

Patients will have no direct benefit from participating in this study. Both perioperative pain management treatment options are standard of care at SJHM. Exparel® is approved by the FDA for abdominal wall infiltration for perioperative pain management, but is not on pharmacy formulary at this institution because of cost. If this study demonstrates benefit to Exparel® utilization in TAP Blocks, it will very likely become formulary.

Listed below are the descriptions and risks of TAP block with Exparel® and epidural.

TAP Block

Exparel®: General

Bupivicaine is a local anesthetic commonly used and standard of care for pain management with epidural catheters and transversus abdominis plane regional blocks. Exparel® is a long acting form of bupivicaine. The Exparel® dose used is 266 mg. The adverse event profile is as follows: The most commonly encountered acute adverse experiences to bupivacaine and all amide-type local anesthetics that demand immediate counter-measures are related to the central nervous and cardiovascular systems. High plasma concentrations of bupivacaine can occur from overdosage, unintended intravascular injection, or accumulation of bupivacaine in plasma secondary to decreased hepatic metabolic degradation of the drug or diminished plasma protein binding capacity due to acidosis, pathologically lowered plasma protein production, or competition with other drugs for protein binding sites. Although rare, some individuals have a lower tolerance to and are supersensitive to bupivacaine and other amide-type local anesthetics and may rapidly develop signs of toxicity at low doses.

Please see attached Exparel® prescribing information/package insert.

Epidural

The progression of pain fibers blocked by local anesthetics in the epidural space proceeds in the following order from first to last; sympathetic tone, pain, temperature, proprioception, touch and finally motor. As a result there is a dose-dependent relationship between epidural-based local anesthetics and hemodynamic effects, as well as pain control. Sympatholytic dermatomal spread exceeds that of both pain control and that of motor blockade. Significant hemodynamic changes

can result, as venous capacitance increases in the dermatomes blocked. This may result in potential hypotension if intravascular volume is not increased to match this hemodynamic effect. When the dermatomal levels include the cardiac accelerator fibers above T6, bradycardia can also result.

In addition to hemodynamic changes, there are several other potential complications associated with epidural catheters. Inadvertent dural puncture occurs with an incidence ranging from 1-10%. The consequence is a positional headache, requiring the patient to lay supine until symptoms reside. Treatment is usually conservative, however epidural blood patch may be offered if symptoms are refractory to bed rest. Rare but more consequential complications include epidural hematoma and abscess. The American Society for Regional Anesthesia (ASRA) has published restrictions for epidural catheters based on INR, platelet count, and the presence of certain anticoagulants. Epidural abscess can result from epidural placement in a systemically infected patient. Lastly, neuropraxia may result from epidural catheters. However the incidence of this complication is both rare and self-limited (less than 30 days).

Opioids are also used with local anesthetic (LA) in the epidural space for analgesia. Opioids cross the dura rapidly and enter the spinal cord, where it binds with strong affinity to the opioid receptors in the substantia gelatinosa. The lipid solubility is a very important factor that effect the passage of opioids across the dura. Lipid-soluble drugs penetrate the spinal cord rapidly. Fentanyl is the commonly used opioid in epidurals due to it is a potent lipid soluble opioid with a strong affinity for the opioid receptor. Because of the reduced cephalic spread there are less opioid side effects with fentanyl. Pruritus is the most common side effect, while nausea and vomiting are less common. Respiratory depression is very rare and are usually associated with the use of other systemic opioids or its accumulation from an infusion.

10. SURGICAL PROCEDURE DESCRIPTIONS

TAP Block

The technique has evolved from a blind, change-of-resistance method based on surface anatomy to an ultrasound-guided technique, allowing for real-time identification of anatomic landmarks and visualization of local anesthetic spread between the internal oblique and transversus abdominis aponeuroses following injection. For midline incisions and laparoscopic surgery, a bilateral injection technique is advocated.

TAPB relies on the injection of local anesthetic (LA) in the fascial plane between the internal oblique and transversus abdominis. This plane contains the anterior rami of spinal nerves T7-L1, anatomically bounded cranially by the inferior costal margin, and caudally by the iliac crest. These anterior rami terminate in the anterior cutaneous tissue of the abdomen, rectus abdominis muscle, and peritoneum. In the lateral-anterior direction, the mid-axillary line is the starting point for needle insertion. Cadaveric studies have shown that when LA is injected below the umbilicus, it spreads from L1 to T10 superiorly. Supra-umbilical analgesia to T7 can be obtained with an infracostal injection point.

Using the ultrasound-guided method, the patient is positioned supine. The abdomen is prepped and draped in a sterile fashion, with focus on the region between the iliac crest and inferior costal margin. The ultrasound probe is utilized to scan starting at the mid-axillary line, until the peritoneum and abdominal muscles are identified. A four-inch needle is inserted in this plane, until placement between the tranversus abdominis (TA) and internal oblique (IO) is confirmed

by ultrasound. Care must be taken to avoid peritoneal, hepatic, and pleural puncture. Confirmation of needle placement often requires hydrodissection to establish separation of TA and IO muscle layers. Because the nerves follow the plane of needle insertion, analgesia from TAPB relies on volume spread of LA. It is therefore important for the practitioner to select an LA concentration that would allow for the safe injection of 20-25cc per side.

Although TAPB may be accompanied by catheter placement, the block is usually performed in the single-shot fashion. For the purpose of this study, we will use Exparel up to 266mg; as a 1.3% solution that will be diluted to a final volume of 40cc with preservative free normal saline for safe injection (total 20cc or 133mg each side). TAPB with Exparel will be expected to provide up to 72 hours of somatic pain. There is no hemodynamic perturbation associated with the block, and therefore, there is no change in intravascular loading conditions. Neurovascular injury associated with TAPB is exceedingly rare, and when it does occur, the consequences are minimal – sensory and minimal motor block may occur. This is in contrast to epidural anesthesia, which can result in severe sensorimotor deficit. Because there is no sacral involvement with TAPB, bladder catheterization is not required.

Potential rare complications of TAPB include peritoneal puncture, hepatic puncture, splenic puncture and inadvertent femoral nerve blockade. Ultrasound guidance should minimize the incidence of inadvertent solid organ puncture. However, femoral nerve blockade may result even from a technically sound TAPB because fascia iliaca communicates with the transversalis fascia. Other complications include LA toxicity, bleeding, bruising and localized infection.

Surgical pain refractory to a technically successful TAPB is typically visceral or neuropathic in nature, largely due to inflammation that exceeds the dermatomal coverage of the block. Pain may also originate in the upper abdomen, as T7-10 may be insufficiently covered. Typically, non-narcotic adjuncts such as acetaminophen and gabapentin may be required to provide full-spectrum coverage of the pain associated with laparoscopy or peritoneal surgery.

Single shot TAPB for colorectal surgery is standard and customary at this time in the well-established SJMH Enhanced Recovery Initiative. This modality provides analgesia within the context of early mobilization, absence of invasive catheterization, and absence of hemodynamic perturbation.

Epidural

Epidural analgesia is commonly employed for abdominal surgery. Like the TABP, a low thoracic epidural catheter is routine and customary in our practice, and has been effectively used to manage perioperative pain associated with colorectal surgery. In the perioperative period, it provides the patient with surgical site-specific pain control without the systemic side effects of opiate medications. Furthermore, its sympatholytic effects are thought to counteract the ileus induced by surgical manipulation of the bowel. Lastly, the dose can be titrated to achieve the precise sensorimotor blockade required in the postoperative period via a catheter-based infusion.

Epidural Catheterization (EC) relies on the fact that nerve bundles arising from the spinal cord reside in the epidural space. This is a potential space separated from the intrathecal space by the dura. Presynaptic nerve fibers reside in the epidural space, where they provide sensorimotor

innervation from C2 to S4. Opioids placed in this space migrate vertically and laterally, dependent on volume, concentration, and placement of the needle or catheter.

The patient is placed in the sitting position for the epidural technique. After the back is prepped and draped in a sterile fashion, an 18 gauge Touhy needle is advanced following LA infiltration of the skin. The Touhy needle is advanced under loss of resistance technique after it is placed in the longitudinal ligament. Following puncture of the ligamentum flavum, the loss-of resistance should be obtained. The catheter is threaded into the space, and intrathecal (IT) or intravenous (IV) catheter placement is ruled out by test dose (3 cc of 1.5% lidocaine + 5mcg/cc epinephrine). Patient cooperation is required to achieve proper positioning, as well as to rule out potential symptoms of LA toxicity.

At this center, we use fentanyl, 5 mcg/ml, and bupivicaine, 0.0625%. As a result we have achieved sufficient pain control without severe hemodynamic and motor effects. We can then adjust the rate of infusion to match the incisional coverage necessary for functional analgesia.

EC is an effective modality for pain control for both open and laparoscopic bowel resection. It allows titration of somatic, visceral, and neuropathic pain, as well as sympatholysis. Relative to TAPB, it requires closer hemodynamic, fluid, and neurologic surveillance. Close attention to anticoagulant administration must be maintained, as well as ambulatory precautions. In deciding the optimal regional anesthetic for abdominal surgery, the considerations of optimal pain control, risk profile, and surveillance burden must all be weighed. The risk-benefit profile is such that

epidural analgesia is considered safe and effective and is standard and customary at most institutions across the world, including SJMH.

11. STATISTICAL CONSIDERATIONS

The power analysis using NPS scores, we have an effect size of 0.430, which is an index of the size of the mean differences between each day relative to the standard deviation, which is the magnitude of differences among the means for each day over the random variation that is compared to using the F test. The relative difference among the means is 0.430, which is difference in means of 0.43 between each day divided by an f-test standard deviation of 1 (0.22/1 ≈ 0.418). The mean NPS scores vary from day to day, therefore an intervention would need to result in a level of improvement beyond this expected level of variability. This baseline level of variability is represented by an NPS score of 3.6 and so an effective intervention should result in a difference of at least 0.43 compared to the control group. This results in a change greater than 3.63 or less than 2.77 on the point NPS scale. To detect a variation among the mean NPS scale of 0.43 with a power of 0.98, we will need a sample size of 176, of which 53 are lap (30%) and 123 (70%) are open, and 10% (16) was calculated in for anticipated dropouts. All sample size analysis is performed in PASS 13 (Power Analysis and Sample Size System, 2011, Kaysville, Utah).

12. QUALITY CONTROL AND QUALITY ASSURANCE

The research coordinator will meet with the principal investigator monthly during patient enrollment to review the progress of the study and adherence to the study protocol.

13. REGULATORY REQUIREMENTS

Approval for the Institutional Review Board at Saint Joseph Mercy Health System will be completed prior to the initiation of this research. All study team members have completed the CITI research-training program.

14. SCIENTIFIC REFERENCES

1. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290:2455-2463.

2. Gendall KA, Kennedy RR, Watson AJ, Frizelle FA (2007). "The effect of epidural analgesia on postoperative outcome after colorectal surgery". Colorectal Dis. 200 Sep:9(7):584-98; discussion 598-600

3. Mouawad NJ, Leichtle SW, McCord M, Hoskins K, Welch KB, Lampman RM, Cleary RK. Is continuous preperitoneal analgesia effectively equivalent to continuous epidural analgesia for pain control after colorectal surgery? Manuscript in preparation.

4. Keller DS, Ermlich BO, Schlitz N, Champagne BJ, Reynolds HL, Stein SL, Delaney CP. The effect of Transversus Abdominis Plane blocks on postoperative pain in laparoscopic colorectal surgery: a prospective, randomzied, double-blind trial. Dis Colon Rectum 2014;57:1290-97

5. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic effect of Transversus Abdominis Plane block after abdominal surgery: a prospective controlled trial. Anesth Analg 2007;104:193-7

6. Ventham NT, O'Neill S, Johns N, Brady RR, Fearon KCH. Evaluation of novel local anesthetic wound infiltration techniques for postoperative pain following colorectal resection surgery: a meta-analysis. Dis Colon Rectum 2014;57:237-5

7. Candiotti KA, Sands LR, Lee E, Bergese SD, Harzman AE, Marcet J, Kumar AS, Haas E. Liposome bupivicaine for postsurgical analgesia in adult patients undergoing laparoscopic colectomy: results from prospective phase IV sequential cohort studies assessing health economic outcomes. Current Therapeutic Research 2014;76:1-6

8. Lehmann N, Joshi GP, Dirkmann D, Weiss, M, Gulur P, Peters J, Eikermann M. Development and Longitudinal Validation of the Overall Benefit of Analgesia Score: A Simple Multi-Dimensional Quality Assessment Instrument. BJA 2010.

APPENDIX 1. Overall Benefit of Analgesia Score (OBAS)

Patient Name_____ Time_____

FIN_____DOB_____Date of Surgery_____

Please circle correct day.

0. Pre-op 1. POD 0 2. POD 1 3. POD 2 4. POD 3

1. Please rate your current pain **at rest**:				
Minimal Pain				Maximum imaginable Pain
0	1	2	3	4
2. Please grade any distress and bother from vomiting in the **past 24 hours**:				
Not at All				Very Much
0	1	2	3	4
3. Please grade any distress and bother from itching in the **past 24 hours**:				
Not at All				Very Much
0	1	2	3	4
4. Please grade any distress and bother from sweating in the **past 24 hours**:				

Not at All				Very Much
0	1	2	3	4

5. Please grade any distress and bother from freezing in the **past 24 hours**:

Not at All				Very Much
0	1	2	3	4

6. Please grade any distress and bother from dizziness in the **past 24 hours**:

Not at All				Very Much
0	1	2	3	4

7. How satisfied are you with your pain treatment during the **past 24 hours**?

Not at All				Very Much
0	1	2	3	4