IRB Application for Population Health and Quality Research Study

Title of Study: Combined administration of Bupivacaine and Exparel versus Bupivacaine or Exparel alone for postoperative analgesia in posterior lumbar spine surgery - A Prospective Randomized Study

Background and Statement of Context

It is estimated that 1 million elective (inpatient and outpatient) spinal surgery procedures are performed each year in the US, including 464,000 spinal fusions, 342,000 discectomies, and 213,000 laminectomies [1, 2]. Spine surgery is thought to result in severe postsurgical pain for a variety of reasons, including the size of the incision, the damage that may occur to ligaments, muscles, bone, discs, and joints when performing the surgical procedure, the existence of preoperative pain, and opioid-induced hyperalgesia (OIH) that may occur with pre-operative opioid use [3]. OIH may result in sensitization of the dorsal horn of the spinal cord where pain signals are first processed, reducing the threshold required to perceive pain, thereby prolonging and magnifying its effect [4]. Pain following spine surgery is thought to be most intense after a few hours, gradually subsiding over a few days, as supported by pain severity scores recorded in studies of various approaches to managing postsurgical pain [5]. Uncontrolled postsurgical pain results in delayed mobilization and consequently longer length of hospital stay (LOS) and morbidity associated with bed rest, increased opioid usage, and lower patient satisfaction.

A variety of approaches are currently used to manage postsurgical pain, including pre-emptive analgesia, systemic analgesia, regional analgesia, and local analgesia [6]. These approaches are often combined in a multimodal regimen intended to address the various components of postsurgical pain, including nociceptive, neuropathic, and inflammatory mechanisms [7]. Many of the current approaches to managing postsurgical pain require use of opioid analgesics such as morphine, fentanyl, hydromorphone, hydrocodone, or oxycodone [8]. Many of these approaches provide only temporary pain control since the medications used have a short duration of effectiveness [9, 10]. Repeated or continuous dosing is therefore necessary to extend their effectiveness, which must be administered by clinical staff (e.g. IV or IM bolus), Patient Controlled Analgesia (PCA) device, elastomeric pump, or taken orally when permitted (e.g. after regaining gastrointestinal motility).

Although short-term opioids can be effective to manage moderate to severe pain, they are associated with a variety of opioid related adverse events (ORAEs), including potentially incapacitating side effects and serious adverse events. For postsurgical pain, patients are at greatest risk for ORAEs during the first 24 hours after surgery when their opioid use is highest [11]. The use of opioids to manage postsurgical pain may be of particular concern for spine surgery, since many patients are already using opioids prior to their surgical procedure. This increases the possibility of ORAEs with higher perioperative doses and continued use beyond the perioperative period [3]. In addition, consumption of opioids is often an outcome measure in spine surgery, and continued or increased use is considered an indicator that the surgical procedure was not successful [12]. It may therefore be beneficial to minimize the amount of opioids consumed for postsurgical pain.

Given the limitations of current approaches to managing postsurgical pain, as well as the consequences of not adequately managing pain following surgical procedures, researchers are continually developing and investigating new approaches that provide optimal pain management. Postsurgical pain management regimens are also being evaluated and refined as a component of broader enhanced recovery after surgery (ERAS) initiatives intended to improve outcomes, reduce hospital LOS, and promote return to normal activities following elective surgical procedures [13]. These initiatives generally favor approaches to manage postsurgical pain that may increase early ambulation and discharge (e.g. regional or local analgesia with local anesthetics) while discouraging those that may decrease them (e.g. IV PCA with opioids).

Approved by the FDA in 2011, Exparel (liposomal bupivacaine) is a sustained-release version of the local anesthetic bupivacaine. While bupivacaine may last 6 to 12 hours to provide post-surgical relief, it is claimed that Exparel can last up to 72 hours after local infiltration at the surgical site [14]. Different studies have also compared the efficacy of Exparel to bupivacaine for the management of postsurgical pain following various surgical procedures, including inguinal hernia repair, breast augmentation, and TKA [15-20]. While some of these studies have supported the efficacy of Exparel to provide superior relief of postsurgical pain, others have found bupivacaine to be just as effective [20]. There is still however, a paucity of literature on the efficacy of Exparel for spine surgery pain management.

Study Questions/Objectives and Hypothesis

This study is aimed at prospectively examining clinical and economic outcomes when managing postsurgical pain using local infiltration of Exparel for patients undergoing primary, 1 or 2 level, lumbar laminectomy with or without fusion. There is a growing body of evidence suggesting that combining Exparel with a short acting numbing medicine gives much better pain coverage. The rationale is that Exparel can take several hours to have anesthetic onset and conventional thinking believes that if we can cover the immediate postoperative pain better with an immediate acting anesthetic to bridge the onset gap, then better outcomes will be achieved. The combination of these medications have been used in various studies previously in other areas of the body both in orthopedics and non-orthopedics and no adverse effects of combining these medications and in similar quantities/dosing have been observed [22,23,24]. To this end, we hypothesize that compared to patients that only received local infiltration of bupivacaine or only administered Exparel, the intervention group treated to a combination of Exparel and bupivacaine would, during their hospital stay following surgery, experience:

1. Reduced mean postoperative pain score (Wong-Baker pain faces scale of 0-no pain, to 10-extreme pain)
2. Reduced total consumption of opioids (in mean morphine equivalents)
3. Reduced overall cost of postoperative pain control medications
4. Decreased incidence of ORAEs

5. Reduced time to achieve physical therapy discharge criteria (criteria set according to each patient's living situation, preoperative physical function, comorbidities, and other goals)

6. Reduced inpatient length of stay (LOS)

Study Benefits to Virtua

This study could potentially benefit Virtua in several ways. If Exparel is shown to reduce postoperative pain for spine surgery patients, and consequently reduce their opioid consumption for postoperative pain management, then there could be the potential to see an improvement in patient satisfaction with regards to pain management. In addition, Virtua could stand to gain some cost savings if Exparel is shown to support decreased incidence of ORAEs such as respiratory depression, leading to reduced time to physical therapy discharge criteria and consequently reduced LOS.

If on the other hand, the study indicates that the more expensive Exparel is no more effective at managing postoperative pain compared to the cheaper alternatives, then Virtua stands to directly gain significant cost savings by adopting the use of the cheaper options as standard practice.

Study Methodology

Patients who meet all of the following inclusion criteria may be eligible to participate in the study if:

1. Age 18 or older;

2. Primary indication is low back pain, lumbosacral radiculopathy, lumbar disc degeneration, lumbar disc herniation, stenosis, spondylolisthesis, spondylolysis, or deformity requiring surgical intervention;

3. Scheduled to undergo primary, 1 or 2 level, posterior lumbar laminectomy with or without fusion, discectomy with fusion, or fusion at Virtua Memorial Hospital;

4. Willing to provide informed consent, participate in study, and comply with study protocol.

Patients who meet any of the following criteria may not be eligible to participate:

1. Hypersensitivity or allergy to local anesthetics;

2. Pregnant or contemplating pregnancy prior to surgery;

3. Previous surgery in lumbar spine (i.e. other than microdiscectomy);

4. Prior treatment for alcohol, recreational drug, or opioid abuse;

5. Serious spinal conditions (e.g. spinal cord compression, cauda equina syndrome, spinal infection, spinal tumor, spinal fracture, inflammatory or systemic spinal arthritis);

6. Surgery involving more than 2 vertebral levels;

7. Worker's compensation or personal injury related to lumbar spine (treatment outcomes may be affected by patient's personal interests [21]; could also run into potential issues with reimbursement).

8. Lactating women

9. Patients with end stage liver disease

During the preoperative office visit, the surgeon will inform patients that appear to meet study eligibility criteria, about the study, and discuss the differences between the three postoperative pain management alternatives, including their potential risks and benefits. The surgeon will make clear to the patient that consenting to be a part of the study means that the patient has agreed to be randomly assigned to one of the three postoperative pain management groups. The patient would be told that the random assignment is going to be determined by rolling a standard die. The patient would be informed that the patient's pain would be controlled regardless of group assignment and that no placebos would be used.

Patients who agree to learn more about the study will be approached by a designated and trained study physician assistant (PA), briefly informed about the study, and asked if they wish to complete the screening questionnaire (Appendix 1) to see if they may be eligible to participate. Once the screening questionnaire is completed by the patient, it will be reviewed by the PA to ask any required clarifying questions and obtain additional information to determine eligibility. Participants who appear to meet eligibility criteria will be reviewed by the PA with one of the study investigators prior to confirming if they are eligible to enroll in the study.

Patients who are deemed eligible to participate in the study and are willing to participate will be asked by the PA to complete the research informed consent. This document will be summarized verbally by the PA and potential participants will be given the opportunity to ask questions about the protocol or their involvement prior to providing consent. Those who agree to participate and provide research informed consent will be enrolled in the study, and given a copy of the research informed consent document. The patient's informed consent would be added to the patient's chart.

On the day of surgery, in the operating room, the circulating nurse will roll a die to randomly assign the patient to one of the three pain management groups. The study intervention group (die roll outcome 1 or 2) will receive a local infiltration of EXPAREL and bupivacaine 0.5% w/v solution into the surgical site (1 level patients – 20 mL Exparel + 30 mL bupivacaine 0.5% w/v solution; 2 level patients – 20 mL Exparel diluted to 40mL + 30 mL bupivacaine 0.5% w/v solution). The two medications will not be combined in the same syringe to minimize the possibility of a direct interaction between the two. While to date, no such interaction has been confirmed, we will maintain a strict "no mixing of bupivacaine and Exparel in the same syringe" policy throughout this study. The second group (die roll outcome 3 or 4) will only be administered local infiltration of Exparel (1 level patients – 20 mL Exparel; 2 level patients – 20 mL Exparel diluted to 40 mL). The third group will be treated to a local infiltration of 30 mL bupivacaine 0.5% w/v solution. Anesthesiologists will use their usual pre-operative and intra-operative techniques for all study participants and both study groups will receive nurse-administered rescue opioids as needed.

The patients and all staff, including hospital nursing staff, case management, and physical therapists, will be blinded as to which pain management treatment the patient received. While the surgical team cannot be blinded because the appearance of the drugs is different, they will however, not be assessing the outcome measures.

The primary outcome in this study will be the mean postoperative pain score derived from the pain scores recorded by the nursing staff in each participant's clinical records using the visual analog scale of 0-no pain to 10-extreme pain, several times in each 24-hour period, for the entire duration of the patient's hospital stay. Adopting [20] assumptions of a target reduction in mean overall postoperative pain scores of 1 point on the VAS and our anticipated variance of 2, it is estimated using one-way analysis of variance that for a statistical power of 80% and significance level of 0.05, a minimum of 40 participants will be required in each study group for a total of 120 study participants. To minimize the possibility of dropouts or incomplete data impacting the analysis, a minimum of 45 participants will be enrolled in each study group, for a total of 135 enrollees.

Secondary outcome measures in this study include total opioid consumption. All opioid analgesics used in the hospital will be recorded in the participant's clinical record, including: Name of medication (e.g. morphine); Dose administered (e.g. 10mg); Route of administration (e.g. IV, IM, oral); Reason for administration (e.g. surgical site pain). All opioid analgesics will be converted into oral mg morphine equivalent to determine the total dose of opioids used during the hospital stay using the conversion factors in Appendix 2. Other secondary outcome measures include mean time to achieve physical therapy discharge criteria, mean LOS, and incidence of ORAEs. ORAEs will be documented using the checklist shown in Appendix 3 with assistance from a nurse during every nursing shift (i.e. every 12 hours) until hospital discharge).

Means will be compared among all the three arms using analysis of variance, proportions will be compared using chi-square tests, and logistic regression will be used to analyze for confounding effects. All statistical analyses will be conducted in Minitab 16 Statistical Software.

Protection of Human Subjects

Throughout the study, the principal investigators (Virtua Memorial spine surgeons and PAs), will be the only ones with access to the data collection database. Following the completion of the study, all personal health information collected, including name, gender, age, significant medical comorbidities, and postoperative complications, will be de-identified as soon as possible prior to data analysis and any subsequent publications or research submissions. Patient would be told participation is purely voluntary with no monetary reimbursement and minimal risk of being assigned to one of the three pain management groups.

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Appendices

APPENDIX 1. SCREENING QUESTIONNAIRE

Participant information

Last name		**Date of birth**	/ /
First name		**Age**	

Contact information

Home phone	**( ) -**	**Cell phone**	**( ) -**
Home street address			
Home city, state, Zip			
Email			

Inclusion criteria

#		Yes	No
1	Are you able to speak, read, and write in English?		
2	Are you able to speak, read, and write in Spanish?		
3	Do you have low back pain, radiculopathy, disc degeneration, disc herniation, stenosis, spondylolisthesis, or mild deformity?		
4	Are you scheduled for lumbar spine surgery at Virtua Memorial Hospital in the next 30 days?		
5	Are you willing to participate in the study and comply with the study protocol?		

Exclusion criteria

#	Question	Feet	Inches
1	What is your current height?		
2	What is your current weight?	Lbs.	
		Yes	**No**
3	Have you ever been diagnosed with a mental health conditions such as anxiety or depression?		
4	Are you currently taking medication for depression, anxiety, or any other mental health condition (e.g. Prozac, Xanax, Ativan, Zoloft)?		
5	Have you ever been treated for alcohol, recreational drug, or narcotic medication abuse?		
6	Have you ever had an allergic reaction to any type of local anesthetic such as lidocaine, procaine, or Marcaine®?		
7	Have you ever had spinal fusion surgery (e.g. rods, screws, cages, implants) before?		
8	Have you been taking opioid analgesics (also known as narcotics) such as Vicodin, Percocet, or OxyContin for more than 30 days?		
	Females only:	**Yes**	**No**
9	If you are female are you currently pregnant, or do you plan on becoming pregnant before your surgery?		

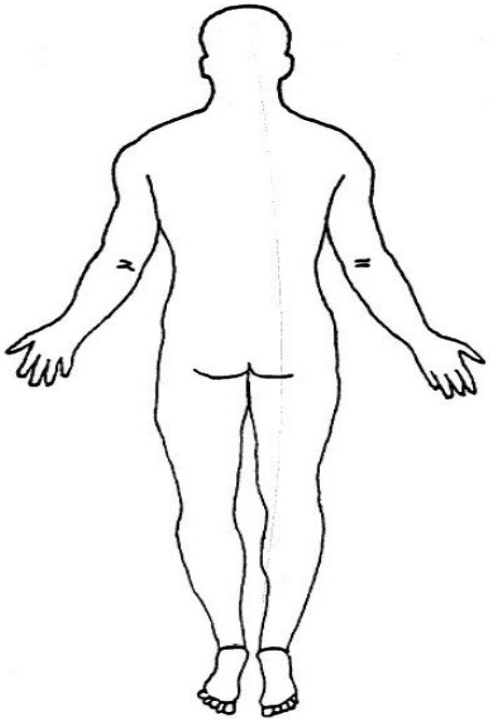
Pain diagram

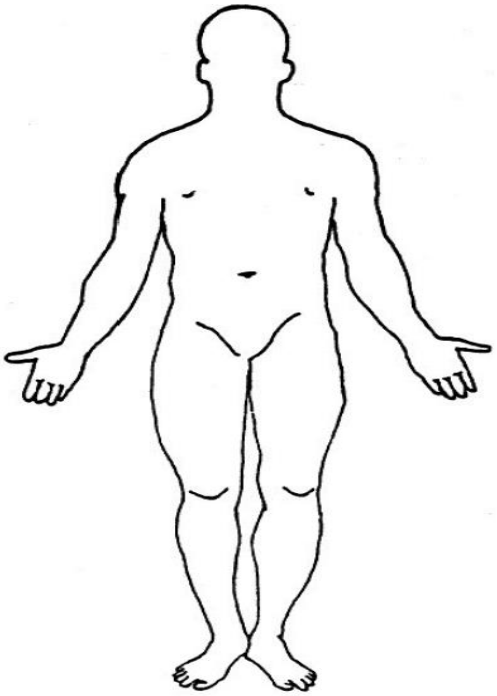
Instructions

Please indicate where you currently have pain in your body.

Please use the marks below to indicate each type of symptom you may have.

ACHE	NUMBNESS	PINS & NEEDLES	BURNING	STABBING
^ ^ ^ ^	**O O O O**	= = = =	**X X X X**	/ / / /
^ ^ ^ ^	**O O O O**	= = = =	**X X X X**	/ / / /





BACK **FRONT**

Pain medication questionnaire

Instructions

Please indicate if you have taken any of the following medications for pain in the past month:

Brand name	**Generic name**	**Yes**	**No**
Actiq	Fentanyl transmucosal		
Advil	Ibuprofen		
Aleve	Naproxen		
Avinza	Morphine extended-release		
Bayer	Aspirin		
Butrans	Buprenorphine transdermal		
Celebrex	Celecoxib		
Codeine	Codeine		
Darvocet	Dextropropoxyphene		
Darvon	Propoxyphene		
Demerol	Meperidine		
Dilaudid	Hydromorphone		
Dolophine	Methadone		
Duragesic	Fentanyl transdermal		
Embeda	Morphine / naltrexone extended release		
Exalgo	Hydromorphone extended release		
Excedrin	Acetaminophen / aspirin / caffeine		
Fioricet	Butalbital / acetaminophen / caffeine		

Fiorinal	Butalbital / aspirin / caffeine		
Flexeril	Cyclobenzaprine		
Kadian	Morphine extended-release		
Levo-Dromoran	Levorphanol		
Lorcet	Hydrocodone / acetaminophen		
Lortab	Hydrocodone / acetaminophen		
Lyrica	Pregabalin		
Morphine	Morphine		
MS Contin	Morphine controlled release		
Neurontin	Gabapentin		
Norco	Hydrocodone / acetaminophen		
Nucynta ER	Tapentadol extended-release		
Opana	Oxymorphone		
Opana ER	Oxymorphone extended-release		
OxyContin	Oxycodone		
OxyContin CR	Oxycodone controlled release		
Percocet	Oxycodone / acetaminophen		
Robaxin	Methocarbamol		
Skelaxin	Metaxalone		
Soma	Carisoprodol		
Toradol	Ketorolac		
Tylenol	Acetaminophen		
Tylenol #3	Acetaminophen / codeine		
Ultracet	Tramadol / acetaminophen		
Ultram	Tramadol		
Vicodin	Hydrocodone / acetaminophen		
Voltaren	Diclofenac		

APPENDIX 2. CONVERSION FACTORS FOR COMMON OPIOID ANALGESICS TO ORAL MORPHINE EQUIVALENTS

Drug	**Route**	***Approximate Equianalgesic Dose (mg)**	****Morphine Equivalent Dose (MED) Factor**
Codeine	Oral	200	0.15
Fentanyl	Parenteral	0.1	300
Hydrocodone	Oral	30	1.00
Hydromorphone	IM	1.5	20
Hydromorphone	Oral	7.5	4
Morphine	IM/IV	10	3
Morphine	Oral	30	1
Oxycodone	Oral	20	1.5
Oxymorphone	IM	1	30
Methadone	Oral	7.5	4

* Equivalent to 30 mg of oral morphine (Source: http://www.globalrph.com/narcotic.htm)

** 1mg of the drug converted to equivalent mg of oral morphine

APPENDIX 3. INCIDENCE OF OPIOID RELATED ADVERSE EVENTS

Instructions
Please indicate if you have experienced any of the following symptoms in the past 12 hours:

Symptom	Yes	No	Comments
Constipation			
Falling			
Hypoxia			
Lethargy			
Nausea			
Postoperative ileus			
Respiratory depression			
Sedation			
Somnolence			
Unsteadiness			
Urinary retention			
Vomiting			