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EXPAREL COMPARED TO STANDARD BUPIVACAINE
FOR POSTOPERATIVE ANALGESIA
FOLLOWING LUMBAR SPINE FUSION

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

July 31, 2020

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Abstract

Inadequate postoperative pain management following spinal surgery contributes to delayed mobilization and chronic pain. The current standard of care following spinal surgery consists of opiates and anesthetics to target multiple pain pathways. However, opiates are limited by their significant adverse effects and anesthetics are limited by their short duration of delivery. One approach that may overcome these limitations is liposomal or lipid-encapsulated drug formulations, which have been shown to extend the duration of drug delivery to target tissues. **In this study, we will compare adjunctive opioid consumption in a randomized controlled trial of patients undergoing elective posterior lumbar spinal surgery that receive liposomal and conventional anesthetic versus conventional anesthetic.** We hypothesize that liposomal anesthetic will improve pain management by reducing the total adjunctive opioid consumption required. This study will address a key limitation of conventional anesthetics and may provide evidence for the utility of liposomal anesthetic in postoperative pain management.

Chapter 1: Introduction

1.1 Background

A. Spinal degenerative disease

Spinal degenerative disease (SDD) continues to be a common and disabling medical problem as diagnosis rates increased 4% from 1997 to 2005 in the United States.¹ The progressive accumulation of natural or incidental stressors on vertebrae and discs propagates the risk of developing a degenerative changes and onset of back pain.

The spinal column is composed of vertebrae, intervertebral fibrocartilage or discs, and a spinal canal collectively formed by vertebral foramen. The primary pathophysiology stems from initial degenerative changes to the intervertebral discs, such as loss of height and decreased proteoglycan and water content within the disc.² Subsequent breakdown within the discs results in spondylosis, which causes severe discogenic pain frequently experienced in the paraspinal region and exacerbated by movement.² Furthermore, failure of the discs to maintain separation between vertebrae contributes to altered loading patterns and distribution of weight along the vertebrae.¹ The resulting loss of stability along the vertebrae can cause fracture of the vertebral arch or a condition known as spondylolysis. Eventually, chronic degeneration of the discs results in loss of the cartilaginous buffer between two vertebrae and can lead to spondylolisthesis or slipping of a vertebra past the vertebra inferior to it. In addition to disc degeneration, deterioration of the vertebrae affects the spinal canal and traversing neurological tissues.¹ Spinal stenosis, or narrowing of the spinal canal, is a prominent sequelae of degeneration due to stress on the spinal cord from impingement by deteriorating bony prominences of the vertebrae³ or by contents bulging from ruptured discs.² Due to upstream compression of the spinal cord, patients can experience peripheral neuropathies or loss of distal motor and sensory functions.

Furthermore, impingement can create stress on traversing neurological tissues branching from the spinal canal that can also result in a subset of radicular neuropathies.³

B. Low back pain

Structural changes in spinal anatomy cause a majority of unspecific back pain.² The severity of pain reflects the dense multitude of muscle, soft tissue, and nerve fibers that are affected by SDD. Most patient-reported back pain can be diagnostically confirmed with MRI imaging.⁴ Furthermore, incidental findings of degeneration have shown to be associated with an increased risk of developing back pain.⁵ Back pain has become one of the most common reasons^{6,7} and primary symptom that compels individuals to consult a doctor.^{2,8} Initial onset of back pain occurs between the ages of 30 to 40 years old with almost 60% of patients reporting some form of unspecific back pain when seeing their primary doctor.² Back pain reported by patients is not only prevalent but significant as it's ranked number one for cause of disability in 45 developed countries and 94 developing countries.¹ The lower lumbar region seems to be the most commonly area affected, which parallels the higher rates of lumbar degeneration.^{1,4} In a study done by Buser et al. looking at spinal degenerative trends, diagnosis of lumbar degeneration was almost two times more prevalent then diagnosis of cervical degeneration throughout different age groups and over time.¹ Furthermore, imaging studies done by de Bruin et al. report that degenerative changes were predominantly found in the lumbar spine.⁴ As a result, lumbar spinal degeneration is often implicated as the cause for what has been termed as "low back pain" (LBP).⁹ In a review by Barrey et al., analysis of the classification of chronic LBP based on injury modality was conducted and their findings support renaming unspecific chronic LBP to degenerative chronic LBP given this profound association.⁷

C. Radicular pain and radiculopathy

In addition to experiencing low back pain proximal to the area of spinal degeneration, patients may also report abnormal sensation, weakness, and pain in their legs due to nerve compression. Radicular pain is a common presentation that is due to compressed and inflamed dorsal roots or their respective ganglions that arise from the spinal cord. Irritation of these structures causes irradiated pain along the nerve root without compromise of any neurologic function.³ Patients may describe this pain as a “pain that shoots down their leg.” On the other hand, radiculopathy can also occur in the absence of pain, in which nerve conduction from the nerve root is disturbed leading to paresthesia or motor weakness.³ Due to the pathophysiology of degenerative changes leading to inflammation and compression at the nerve root, nerve impairment in radiculopathy is often seen in a dermatomal or myotomal pattern.³ Patients will often describe this as numbness, tingling sensations, loss of sensation, and loss of strength in their lower extremities. Presentation of nerve compression symptoms can be an indication of SDD and may serve as a reason for surgical treatment.

D. Surgical treatment of SDD

Since 1970, the standard has been to trial six weeks of conservative treatment¹⁰ with updated reviews supporting anywhere from four to eight weeks of non-surgical therapy before opting for surgery.¹¹ Progression of LBP to chronic and recurrent episodes requires consideration of surgery as a definitive treatment when conservative attempts do not significantly improve pain. Spinal fusion or spondylodesis or spondylosyndesis has been the accepted surgical procedure utilized in treating chronic LBP.¹² First introduced by Hibbs and Albee in 1911, spinal fusion was a common procedure for treating deformity, trauma, and degeneration of the spine.^{13,14} This approach involves correcting the degenerative anatomy, reducing stress on

neighboring structures, and establishing stability of the affected spinal column.¹⁴ Posterior lumbar fusion (PLF) or approach from the posterior spine has been the conventional method and most orthopedic surgeons are well trained in it. Studies have shown development of new techniques with anterior approach that provide similar initial functional and fusion outcomes.¹⁵ However, there is mixed data showing shorter surgery time with anterior approach,¹⁵ yet higher rates of reoperation and postoperative morbidity when compared to posterior approach.¹⁶ Spinal fusion has become the standard for treating SDD,¹⁴ for which it has become the most common surgical indication.¹³ Systemic reviews regarding lumbar spinal fusion as a surgical treatment of chronic LBP due to SDD done in 2013 and 2017 support its application; fusion remains a viable treatment that reduces pain and produces positive results in carefully and properly selected patients that meet surgical indication, which includes presence of chronic debilitating LBP and accurate diagnosis of degenerative changes.^{17,18} Therefore, surgical treatment is primarily reserved for patients experiencing LBP that is either refractory to conservative efforts¹⁹ or producing focal neurological disabilities.² The use of pathoanatomical diagnosis of SDD via radiological imaging as a supplement of debilitating LBP has established a proper role for lumbar spinal fusion with good outcomes.⁹

E. Postoperative pain following spine surgery

Spinal surgery is a major invasive treatment that commonly results in postoperative pain during rehabilitation. Postoperative pain remains an underestimated²⁰ and undertreated condition despite being a main predictor of chronic morbidity.²¹⁻²⁴ Amongst the 73 million surgeries performed annually in the United States, over 80% of patients experience acute pain after surgery,^{21,25} with most reporting “severe postoperative pain.”^{20,21,25} However, the prevalence of postoperative pain varies across surgical specialties, with spine surgery and more specifically

spinal fusion being associated with the highest pain scores.²⁰ The distinct severity of this pain can be attributed to the extensive amount of dissection through multiple tissue layers that is required. The redeeming factor is that this postoperative pain is transitory and has been shown to gradually improve over an average time period of three days.^{26,27}

F. Consequences of inadequate postoperative spinal surgery pain relief

Although the presentation of postoperative spinal surgery pain is temporary, untreated acute pain contributes to multiple consequences over time. In the immediate postoperative period, insufficient pain relief can prevent achievement of optimal surgical outcomes.²⁴ The three day timetable affords a window of opportunity for proper postoperative pain management in order to facilitate early ambulation and reengagement of the spinal muscles in order to promote “return of normal gait” and “optimal range of motion.”^{27,28} Delayed mobilization also extends hospital length of stay and increases the likelihood of subsequent complications from prolonged bed rest such as deep vein thrombosis or pneumonia.²⁹ In the period following discharge, untreated postoperative pain results in chronic pain, which is associated with significant morbidity.³⁰ Many patients suffer decreases in quality of life and ability to carry out activities of daily living.^{23,31} Eventually, these effects can persist years after the initial surgery and have been shown to cause residual low back pain and lower extremity paresthesia. This set of symptoms, better known as Failed Back Surgery Syndrome, continues to impede patients’ physical function and ultimately reflects failure to improve their original back pain.^{32,33}

G. Multi-modal analgesia (MMA) for postoperative spinal surgery pain

Currently, an exhaustive list of pain management therapies exists for postoperative spinal surgery pain. This is due to the various tissue types that are disturbed during the operation such as vertebrae, nerve root sleeves, fascia, and muscles, which can lead to an overlap in activation

of nociceptive, neuropathic, and inflammatory pain mechanisms.^{27,34} To engage the various pain etiologies, clinical guidelines recommend multi-modal pain management³⁵ that includes narcotic analgesics, NSAIDs, gabapentinoids, corticosteroids, muscle relaxants, and local anesthetic analgesics in order to deliver a synergistic approach to pain.^{27,34}

H. Dependence on opioids despite the associated risks

The predominant limitation in the current standard of care regimen are the numerous and significant adverse effects of opiates, which range from nausea, vomiting, and constipation to respiratory depression, development of tolerance, and “other central nervous system issues.”^{27,34} While the period of treatment with opioids may be short due to the transient nature of postoperative pain and adverse effects may be deemed unsubstantial or necessary because opioids are extremely potent in their analgesic abilities, these acute adverse effects have been shown to negatively impact patients’ recovery.³⁶ In addition, the more specific adverse effect of development of opioid tolerance has been shown to contribute to the development of opioid addiction through increased opioid requirements.^{37,38} This is reflected in the 9.8% of total opioid prescriptions written in 2012 by surgeons as their role as opioid prescriber grows.³⁹ Patients’ long term safety must be considered due to the reported risk of transitioning to prescription opioids following discharge from the hospital to maintain developed opioid tolerances and requirements.

I. Redefining local anesthetics’ role in MMA

In an effort to move away from opioid dependent multi-modal treatment plans, the need for non-inferior or superior non-narcotic pain management options is elicited. This change has been met with increased attempts in redefining the utility of local anesthetic analgesia. Within the past 5 years, short-acting local anesthetics like bupivacaine has shown high efficacy and

smaller side effect profiles when compared to opiates in management of postoperative pain.⁴⁰

However, the narrow duration of action poses an issue due to inadequate coverage of the total length of acute postoperative pain³⁴ and promotes higher peak concentrations of drug, which can lead to unwarranted local and systemic side effects.

J. More adequate treatment of acute postoperative spinal surgery pain duration

Liposomal bupivacaine (LB) or EXPAREL was initially approved by the US Food and Drug Administration (FDA) in 2011 for “local anesthetic use by wound infiltration” for hemorrhoidectomy or bunionectomy. Since then, its utility has been expanded in 2015 when the FDA approved its use in local surgical infiltration.⁴¹ This novelty allows a potential role for LB’s design in not only combating the problems associated with short-acting local anesthetics, but also providing the benefits of bupivacaine.⁴² The new formulation is an amide-based local anesthetic that utilizes a liposomal encapsulated delivery system (DepoFoam) in order to release the medication from a single dose over an extended period of time. Its safety has been proved through initial trials administered on rabbits and dogs.^{43,44} LB’s efficacy for the initial 24h⁴⁵ or whole postoperative period⁴⁶ has been demonstrated when compared to placebo. Further studies have highlighted reduced adjunctive opioid consumption, shorter length of stay (LOS), and increased pain relief when matched to intravenous (IV) opioid patient controlled analgesia (PCA).⁴⁷ Trials comparing LB with standard bupivacaine have also shown significant improvements in similar outcomes in other surgical specialities.^{35,48-50} Of note, a few studies have shown noninferiority with regard to pain relief between LB and various local anesthetics.^{46,51-53} Yet despite these results, groups treated with LB alone displayed increased mobility and shorter hospital LOS.^{51,52} Noninferiority of LB to morphine⁵⁴ and bupivacaine does not completely rule out LB’s role in postoperative pain. LB remains a viable option given it

provides similar analgesia without the side effects associated with opiates. There is limited literature on LB's role in spinal surgery. Retrospective matched cohort studies have shown both notable^{55,56} and significant improvements^{57,58} to postoperative pain and opioid consumption, with room to improve their studies. A single RCT reported no significant reduction in adjunctive opioid but utilized a small sample size and single surgical indication.⁵⁹

1.2 Statement of the Problem

Postoperative pain management in spinal surgery has followed a multi-modal approach. While this method is relatively effective in treating the pain that patients feel by way of reduced pain scores, there is a high prevalence of adverse effects related to concurrent opioid use.³⁷ Additionally, the risk of opioid dependence increases with effective standard of care pain management. While local anesthetics for analgesia has demonstrated the same if not superior levels of pain relief when compared to conventional methods, the duration of action does not match up with the estimated 3-day period of acute postoperative pain. Therefore, liposomal bupivacaine offers a unique solution through its DepoFoam technology, which allows for extended release of the encapsulated medication (standard bupivacaine) without compromising the drug contents. The delayed release of medication will also reduce peak drug serum concentrations and help limit local or systemic side effects to the local anesthetic. The lack of consensus in efficacy and absence of more double-blinded prospective randomized controlled trials that are powered sufficiently prompts the need for this study. This problem offers a unique opportunity to extensively evaluate liposomal bupivacaine's role in pain management for spine surgery.

1.3 Goals and Objectives

The goal of this study is to demonstrate that Liposomal Bupivacaine (brand EXPAREL) provides more effective postsurgical pain relief than standard of care in the treatment of patients undergoing lumbar spine fusion. Usual standard of care consists of non-encapsulated local anesthetic, which has been shown to be effective but insufficient in covering the entire three-day period of acute postsurgical pain. Therefore, this trial aims to address these limitations and redefine a role for liposomal local anesthetic in multi-modal analgesic treatment plans.

The primary objectives of the study are to: 1) enroll the appropriate amount of study subjects that fit the eligibility criteria in order to properly power the trial; 2) compare postsurgical opioid consumption through 72 hours in patients receiving local infiltrative analgesia (LIA) with EXPAREL admixed with bupivacaine HCL (experimental group) to that of patients receiving standard of care (control group) where both groups are also receiving standardized perioperative multi modal analgesia (MMA); 3) test whether there is improvement in the postsurgical pain throughout the total timeframe (3 days) of acute pain following spinal surgery when treated with EXPAREL admixed with bupivacaine HCL compared to standard of care where both groups are also receiving standardized multi modal pain regimens.

The secondary objectives of the study are to: 1) compare safety and efficacy outcomes following LIA with EXPAREL admixed with bupivacaine HCL versus standard of care in patients undergoing elective posterior lumbar spine fusion; 2) compare health outcomes following LIA with EXPAREL admixed with bupivacaine HCL versus standard of care in patients undergoing elective posterior lumbar spine fusion.

1.4 Hypothesis

Local infiltrative analgesia with Liposomal Bupivacaine HCL 1.3% (EXPAREL) admixed with Plain Bupivacaine HCL 0.5% will have a statistically significant difference in post-operative (0-72 hours) mean total dose of opioid rescue when compared to Plain Bupivacaine HCL 0.5% in adults undergoing elective lumbar posterior spine fusion.

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Chapter 2: Review of the Literature

2.1 Introduction – Literature Search Criteria

An extensive search and review of the published literature was done in the time period between December 2019 and June 2020. This search employed the use of electronic journal databases such as PubMed, Ovid Medline, Scopus, and Cochrane. In order to properly identify high-quality articles appropriately relevant to the proposed study regarding, key search terms were used to highlight studies that could provide insight on topics such as background on the clinical problem, current standard of care, alternative study attempts at demonstrating a role for the experimental variable, rationale for conducting the proposed study, possible confounding variables to avoid, input for formulating inclusion and exclusion criteria, and known acceptable primary and secondary outcome measures. Key search terms include (spin* adj2 surger*).mp., exp Anesthetics, local/, exp Bupivacaine/, liposomal bupivacaine.mp., esp Pain, Postoperative/, local infiltration analgesia.mp., multi modal analgesia.mp., low back pain.mp., opioid.mp., (spin* fusion).mp., rates.mp., confounders.mp., risk factors.mp., spinal degeneration.mp., esp Pain, Perioperative/, management.mp., and various combinations of the descriptors listed.

2.2 Overview of Postoperative Pain and its Sequelae

The growing prevalence and incidence of degenerative changes to the spine remains a significant issue.¹ The magnitude and scale of morbidity caused by SDD is more apparent when looking at the prevalence of LBP and associated radiculopathy. Over a lifetime, greater than 70% of people in developed countries report experiencing LBP at one point throughout their lives.^{2,3} Amongst all adults, 15 – 45% note they suffer from LBP² and 85% of adults under the age of 45 have experienced one episode of LBP that required treatment during their lifetime.⁴ The importance of properly treating the highly prevalent condition of LBP is to prevent impairment.

In a 2010 study done by *The Lancet*, musculoskeletal disorders were ranked 2nd behind mental and behavioral disorders for most common etiology causing years lived with disability (YLDs), a hallmark of measuring disability.⁵ More specifically, the category of diseases termed “low back pain” made up a significant portion of the musculoskeletal disorders that lead to increased YLDs.⁵⁻⁷ The development of disability is further seen in a subsequent Global Burden of Disease study published in 2013 that reported LBP as the number one cause for YLDs with an increase of over 56.75% between 1990 and 2013.¹ Disability directly affects peoples’ ability to carry out activities of daily living (ADLs) and contribute to society, which subsequently puts them at risk for development of depression and comorbidities.³ This is evident by epidemiological data collected in 2003 by a French agency that defines healthcare targets that shows LBP was the “leading cause of sick leaves, whose mean duration was 33 days, resulting in 3,600,000 days of work lost per year”.⁸ The lack of improvement with conservative methods and presentation of chronic or refractory low back pain⁹ has been met with improvement by spinal fusion surgery when adequate degenerative changes are diagnostic on imaging.^{7,10} These trends reflect the growth of spinal fusion and the relevance in optimizing perioperative MMA used.

Evaluation of LBP involves recognizing the contribution of patients’ lifestyles and risk factors that cause incidental stress on the spine.¹¹ These include occupational exposure that involves heavy lifting, intense physical work, and obesity, all of which have a tendency to overload the back with repetitive stress on the spinal articular processes.^{2,3} Accumulated insult most commonly falls on the lumbar spine, which highlights the prevalence of lumbar degeneration and LBP. While the risk factors mentioned above are mitigatable, natural degeneration from age and everyday activity is unmodifiable^{1,3} and is reflected by increased prevalence of chronic LBP from age 30 to 60 years old.³

While most people present in early adulthood with acute (less than 6 weeks) or subacute (between 6 and 12 weeks) low back pain,¹² multiple studies report between 5% - 23% of those cases develop into chronic low back pain.^{3,4,12} Chronic low back pain, currently defined as greater than 12 weeks, may demand more aggressive treatment if there is a lack of improvement with medication or exercise regimens. The utility of spinal fusion in treating chronic LBP is reflected by its contribution to continually rising rates of spine surgery. Implementation of spinal fusion saw initial increases of over 55% in the 1980s.¹³ This trend was expanded rapidly as fusion rates increased another 77% to 100% between 1996 and 2003^{1,13} and were a predominant proportion of general increases in spine surgery.¹³ By 2003, spinal fusion had become the 19th most commonly performed surgery.¹ More recent studies show that over the course of 10 years, by 2008, spinal fusion utilization had increased another 111% from 64.5 to 135.5 cases per 100,000 adults.¹⁴ More specifically, rate of lumbar spinal fusion for degenerative conditions has tripled in the 1990s,¹³ with an increase of 220% by 2002¹⁵ and rise in utilization from 0.3 to 1.1 per 1000 adults.¹⁶ When compared to cervical and thoracic spinal fusion, rates of lumbar spinal fusion utilization are notably higher at 28.7 cases per 100,000 adults in 1998 with an increase of 140.5% to 69.1 cases per 100,000 adults in 2008.¹⁴ The stark rise in utilization of spinal fusion and more specifically lumbar spinal fusion can be presumed to be a response to increased incidence of lumbar degeneration and prevalence of LBP. The rise of chronic LBP and subsequent use of surgery given its utility in the setting of accurate diagnosis pinpoints an area of impact if this relevant surgical procedure were to be optimized. Focus on lumbar spinal fusion affords the opportunity to address a large sample population and produce greater generalizability.

A. Postoperative spine surgery pain

Despite the efficacy of lumbar spinal fusion as a treatment for properly selected patients, the success of spine surgery is also dependent on management of acute postoperative pain in order to improve surgical outcomes and prevent chronic morbidity. Postoperative pain is generally thought to be the result of direct iatrogenic trauma to nerve fibers or irritation and inflammation to nerve fibers secondary to the trauma.¹⁷ While pain in the postoperative period is a predictable occurrence due to the invasive nature of surgery, the adequate management of it is not. Over the past two decades, patient perceptions of the inevitability of postoperative pain have risen from 77% to 84%.¹⁸ Along with the rise in expectations, the incidence of acute postoperative pain experienced increased as well; 77% in 1995, 82% in 2003, and 86% in 2014.^{18,19} The continued growth in incidence of acute postoperative pain reflects lack of proper management of acute postoperative pain, which contributes to delayed mobility and development of persistent pain. More specifically, studies show 20-40% of surgical patients report that their pain is in the “severe to maximal pain” category^{20,21} and that acute postoperative pain in the initial 24h is still too severe regardless of the amount of tissue trauma.²⁰

Spinal surgery has historically been associated with postoperative pain. The significance of addressing pain following spinal surgery is with respect to the severity of that pain. A comprehensive comparison done by Gerbershagen et al. analyzed postoperative pain intensity across 179 surgical procedures and found that most severe pain encounters were attributed to spinal surgeries, with spinal fusion ranked 2nd highest in terms of “worst pain since surgery” and pain scores.^{21,22} Conventional or nonminimally invasive spinal surgeries are distinct in that in order to access the area of operation an extensive dissection through a series of subcutaneous tissue, bone, muscle, and ligament is required.^{23,24} This undoubtedly causes more substantial

iatrogenic trauma to the various tissues. The resulting irritation, compression, and inflammation occurs in close proximity of the spinal cord and connecting neuronal bundles,²⁴ which correlate to the severity of postoperative spinal surgery pain when compared to that of other surgeries. While severe, this postoperative pain has been shown to only last approximately three days,^{17,24,25} is proportional to the number of vertebrae operated on, and has no significant correlation with location on the spine.^{17,24} The elective nature of spinal surgeries further emphasizes the need for proper pain management in order to more efficiently facilitate the recovery and ambulation of patients undergoing major spinal surgery.

B. Inadequate management of postoperative spine surgery pain

Postoperative pain following spine surgery is frequently underestimated,²¹ which has subsequently led to over 20% of patients²⁰ reporting insufficient pain relief.^{17,21} Despite advances in analgesics and surgical technique to minimize pain, treatment regimens of acute pain have continued to fail patient expectations. Inadequate management of this pain leads to extensive consequences that occur throughout patients' lives.

In the initial post-op inpatient recovery phase, the consequence of untreated acute postoperative pain is prolonged recovery. Pain limits recovery by inhibiting patients' ability to reengage muscles and ambulate earlier, both of which are fundamental to establishing normal motion and gait following surgery.^{24,26} The lack of consistent pain relief protocols to promote early mobilization also prevents patient use of inpatient rehabilitation services and concurrently hinders support of their recovery.²⁷ In addition, the importance of shortening the interval between surgery and initial mobilization relates to decreasing hospital length of stay and prevention of complications²⁸ associated with prolonged bed rest, such as deep vein thrombosis²⁹ from venous stasis, muscular atrophy development from muscle disuse, or susceptibility to

hospital acquired infections.³⁰ While the timetable of postoperative pain following spine surgery averages three days, it is imperative to properly address this pain in order to promote early mobilization and improve surgical outcomes.

The incidence of postoperative pain persists as a widespread issue due it being a “predictor of chronic pain and disability” following discharge.^{31,32} Although temporary, untreated acute pain has profound impacts on long-term quality of life in the months after spinal surgery. This is a direct result of the pathophysiology of postoperative pain. Preliminary inflammation and irritation of neuronal fibers caused by iatrogenic trauma slowly leads to sensitization of the nervous system when inadequately addressed.^{17,28} A sensitized nervous system potentiates pain sensations from pain receptors on affected nerve fibers. Moreover, the pathophysiology leads to chronic postoperative pain in 10-50% of surgical patients.²⁸ Therefore, the importance of reducing the period of acute postoperative pain is evident from the multiple studies that associate untreated acute pain with the development of chronic postoperative pain²⁸ and increased morbidity³³ that results from it. The main sequelae of chronic postoperative pain are its effects on quality of life, physical function, and overall improvement of the original LBP.^{17,28}

The consequences of untreated acute postoperative pain ultimately extend years after surgery. Within an average 3.4 years,²³ approximately 10-40% of spinal surgery patients develop some persistent postoperative pain (PPP)³⁴ or what is commonly known as Failed Back Surgery Syndrome (FBSS). FBSS is defined by significant residual LBP, leg neuropathy, or leg parathesia.^{23,34} The pathophysiology parallels the chronic pain that is caused by desensitized nerve fibers in the months after discharge. Residual LBP in FBSS patients similarly leads to decreases in quality of life and increased utilization of hospitals or pain medication.³⁴ More

importantly, the extent of FBSS frequently results in reoperation within 5 years.²³ The long term effects of untreated acute postoperative pain following spine surgery continue to demonstrate a need to define more effective postoperative pain management.

2.3 Review of the Current Strategy

A. Multi-modal analgesia (MMA)

Historically, management of acute postoperative pain following spine surgery heavily consisted off opiates due to their potency.³⁵ The lack of sufficient literature on the physiological genesis of postoperative pain led to the dependence of opiates to broadly achieve patient satisfaction. Expanded research on the short- and long-term adverse effects of opiates has prompted a shift towards incorporation of more pathophysiology specific analgesics as the standard of care. As established above, the extent of spinal surgery causes iatrogenic trauma to multiple tissue types. This in turn creates significant nociceptive, inflammatory, and neuropathic pain mechanisms. The diversity in causes of postoperative pain following spine surgery has guided physicians towards utilizing a MMA approach to treat this broad pathophysiology.^{28,36}

Current clinical guidelines recommend perioperative MMA when managing postoperative pain following spinal surgery.^{19,37-39} Studies have shown that combining agents with diverse mechanisms of action provides more effective pain relief.³⁵ The aim of this adopted approach is to maximize the benefit from multiple analgesics with higher specificity for the possible pain pathways.⁴⁰ MMA regimens are selected from an assortment of analgesics consisting of NSAIDS, corticosteroids, gabapentinoids, muscle relaxants, acetaminophen, local anesthetics, and opiates to a slight degree. Moreover, these analgesics can be given through various routes, such as parentally, orally, continually infused via catheter or IV, intramuscularly, or via local injection perioperatively. The apparent discord between severe pain prevalence and

pain management offers a unique opportunity for development of a more refined and standardized therapy for treating postoperative spinal surgery pain.

B. Shifting from opiates to local anesthetics

Despite recent and extensive advances in the development of new pain relief methods that utilize varying combinations of local anesthetic analgesia, corticosteroids, and opioids, improvement in patient satisfaction and acute postoperative pain scores has been stagnant.²⁰ A major barrier to adequate management of patients' acute postoperative pain is the notion that effective treatment is synonymous with more adverse effects.²⁰ This attitude is based in the fact that some MMA regimens still incorporate opiates. Adjusting MMA regimens to exclude opiates has helped reduced prevalence of its related adverse effects, but there is a lack of consistent results demonstrating sufficient pain control without opiates.^{35,41}

The importance of reducing the role of opiates in MMA is to develop a regimen that lacks its associated side effect profile. Although, the potency of opiates in treating postoperative pain is well established,³⁵ the numerous adverse effects of opiates can substantially hinder a patients' recovery. Many of these side effects, ranging from primarily respiratory depression, somnolence, urinary and bowel symptoms, and nausea,^{24,42} are also dose dependent, which limits the flexibility of clinicians when prescribing it.^{35,43} Secondary treatment of adverse effects and reduction in ability to ambulate due to opioids ultimately increases length of stay in the hospital and overall recovery from postoperative spine surgery.⁴⁴ More specifically, the development of opioid tolerance from inpatient treatment is a risk factor for addiction. Systemic reviews have shown that incorporation of opioids in perioperative pain management is predictive of the likelihood of opioid prescriptions being written.⁴⁵ These points highlight the need to find alternative analgesic options that are noninferior in order to mitigate the risk from opioid use.

C. Key role of local anesthetics

To that end, there has been increased importance placed on treating the neuropathic pain and subsequent prevention of neuropathic plasticity.²⁸ Two of the main analgesics that target neuropathic pain are gabapentinoids and local anesthetics. Local injection of anesthetics intraoperatively in particular has gained recognition due to its high efficacy and low side effect profile. Moreover, their pain relief following surgeries requiring extensive dissection, such as spine surgery, is well recorded.³⁵ Among the various local anesthetics, bupivacaine has an established role for spinal surgery requiring a short-term inpatient stay. When compared to other local anesthetics, such as ropivacaine or lidocaine, bupivacaine has superior postoperative pain relief and motor and sensory blockade.⁴⁶ Furthermore, bupivacaine's unique lipid profile facilitates slower elimination, which allows for an extended duration of action.^{46,47} Despite its longer duration of action, studies show that dissemination is still too rapid, which leads to inadequate coverage of the three day postoperative period and higher peak drug concentrations.⁴² The possibility of extending bupivacaine's duration of action offers an opportunity to improve its utility in MMA.

2.4 Review of Empirical Studies: Augmenting the Role of Bupivacaine with EXPAREL

A. EXPAREL's extension of local anesthetic duration

The significance of extending bupivacaine's duration of action is reflected by prior attempts that have reported improvement in postoperative pain control. Studies have shown reduced pain scores and delayed use of rescue opiates when admixing of bupivacaine with clonidine⁴⁸ and superior pain relief or consistently lower pain scores with continuous infusion of bupivacaine.^{36,49} However, these methods are susceptible to additional risk of medication interactions and infection respectively.

In order to obtain similar prolongation in duration without the aforementioned risks, liposomal bupivacaine (LB) or brand name EXPAREL has been thought to be a viable option. LB is an extended release form of bupivacaine that was originally approved for local anesthetic use by wound infiltration in 2011 and later for surgical infiltration in 2015.⁵⁰ The new formulation maintains the use of the amide-based local anesthetic, bupivacaine, but incorporates liposomal encapsulation of the drug. Compared with the previous options, LB does not rely on additional medications or machinery. Instead, it takes advantage of the original strength of bupivacaine and delays dissemination with its unique lipid structure. The specific multivesicular liposome delivery system (DepoFoam) is composed of “biodegradable cholesterol, triglycerides, and phospholipids,” which work to protect the integrity of the enveloped drug while slowly breaking down in order to release a single dose of bupivacaine gradually over time.^{50,51} LB has been shown to undergo rapid uptake within hours and displays prolonged release till 96h post-administration,⁵² but the clinical effect of LB at 96h may not be significant.⁵³

Multiple dosages of LB currently exist (89mg, 155mg, and 266mg) with LB (brand EXPAREL) by Pacira Pharmaceuticals having two formulations (133mg/10ml or 266mg/20ml). 266mg/20ml has been approved by the FDA as the maximum dose due to increase in incidence of adverse effects at higher dosages.⁵² In addition, 266mg/20ml dosage of LB saw longer sensory blockade than both 89mg and 155mg of LB.⁵⁴ When compared to bupivacaine, 266mg/20ml LB displayed fewer adverse effects⁵² and shorter motor blockade,⁵⁴ which is relevant to facilitating pain relief and early ambulation of spine surgery patients.

B. Safety of EXPAREL

Safety of LB was preliminarily confirmed in peripheral nerve blocks on rabbits and dogs⁵⁵ and through multiple routes of administration in animals.⁵⁶ In addition, preference for LB

over continuous infusion in MMA given noninferior efficacy reduces the use of invasive catheters and associated risk of adverse iatrogenic infections. In a single blinded RCT done by Brown et al. with N=59, patients receiving a single intraoperative injection of 266mg/20ml LB diluted with 40ml NS showed no significant difference in incidence of adverse effects, which include nausea, emesis, hypotension, and constipation, when compared to an injection of saline.⁵⁷ In addition, a review of 5 surgery types with substantial sample size (N=823) demonstrated equivalent incidence of adverse effects and tolerability between LB (66mg - 532mg) and bupivacaine HCL (75mg – 200mg).⁵⁸

C. Efficacy of EXPAREL across other surgical specialties

Local infiltration anesthetics like bupivacaine have been a pivotal component of perioperative MMA. Approval of LB for surgical infiltration allowed for numerous trials to ascertain its efficacy across various surgical procedures, such as ileostomy,⁵⁹ colectomy,⁶⁰ thoracotomy,⁶¹ ankle fractures,⁶² total knee arthroplasty,^{37,63,64} and hip arthroplasty.^{65,66} The groups studied generally featured adults undergoing elective surgeries. Overall, patients treated with LB have reported increased pain relief, decreased use of adjunctive opiate consumption, and reduced hospital length of stay. Furthermore, follow-up reviews of LB support its utility with reports of noninferiority to bupivacaine possibly due to low quality and volume of evidence⁶⁷ or significant improvement in the similar outcomes throughout different surgeries.⁴¹

Of the earliest studies done with approval for surgical infiltration of LB, the IMPROVE trial is most notable. This was a multicenter prospective cohort study that compared LB-based MMA, which consisted of single intraoperative administration of LB (266mg/20ml in 30ml 0.9% NS), with traditional postoperative IV opioid patient-controlled analgesia (PCA) in the setting of ileostomy. LB-based MMA was correlated with a significant reduction in the primary outcome

of postoperative opioid use (mean, 20mg vs. 112mg; median, 6mg vs. 48mg, respectively; $P < 0.001$).⁵⁹ Although this is a large difference, the primary outcome considered all opioid consumption till discharge or day 30 of the study. Despite that fact, subjects with more poorly treated postoperative pain are subsequently expected to stay longer and use more opioid rescue pain relief. Other significant outcomes include decreases of 2.1 days in postsurgical length of stay ($P < 0.001$) and over \$2000 saved in hospitalization costs ($P = 0.01$). It can be noted that this trial was funded by PACIRA, which is the pharmaceutical company behind EXPAREL, but the design of the study and significant outcomes are still clinically meaningful. MMA consisted of postoperative a single IV administration of ketorolac, and PO acetaminophen 1000mg and ibuprofen 600mg Q6h once no longer NPO. Rescue medication consisted of IV opioid or PO oxycodone 5mg/acetaminophen 325mg Q6h PRN. Despite the small sample size ($N = 27$), which is acknowledged by the authors to be insufficient powering, this data highlighted the utility of a single intraoperative LB injection in reducing dependence on opioid mediated analgesia.

Results of the IMPROVE trial were replicated in open colectomy surgery. A phase 4 single center prospective cohort study also compared LB (266mg/20ml in 40ml of 0.9% NS) based MMA with IV opioid PCA. Once again, significant decreases in the primary outcome of mean total postoperative opioid consumption (57mg vs. 115mg; $P = 0.025$), average total cost of hospitalization (\$8766 vs. 11,850; $P = 0.027$) and median length of hospital stay (2.0 days vs. 4.9 days; $P = 0.004$) were seen in LB based MMA against IV opioid PCA respectively.⁶⁰ The mean total opioid consumption follows the IMPROVE trial in considering all consumption until discharge or day 30, which as mentioned above can obscure results and can be improved upon by limiting measurements to 72h from surgery. Moving needle technique with frequent aspirations

was used to avoid IV injection of LB. Major limitations include underpowering of the study (N=39) and the use of a single surgeon, which may limit recruitment of a diverse sample.

Efficacy of LB was also reviewed in thoracotomy. A retrospective review comparing intercostal blocks (IB) with intraoperative administration of LB (266mg/20ml in 30ml NS) with thoracic epidural analgesia (EPI) showed significant decreases in mean visual analog scale (VAS) pain scores within the IB group on post op day 1 (P<0.04) and day 3 (P<0.04), but not on post op day 2 (P=0.31). Postoperative adjunctive opioid use from 0 to 72h post-op was not significantly different. The discord between decreases in pain scores but not narcotic use reflects a failure to address subjective nature of pain perception, which is a major limitation of the study. However, it can be noted that more patients in the IB group reported a pain score of zero throughout the study and especially on day 3, but the data was barely insignificant (P=0.057).

Success in non-orthopedic surgery justified the possibility for LB to have an impact on orthopedic studies given their high rates of postoperative pain. Davidovitch et al demonstrated the utility of LB (266mg/20ml in 20ml NS) in an RCT (N=76) comparing LB admixed with bupivacaine with saline placebo for ankle fractures requiring open reduction internal fixation surgery. Pain reduction using VAS in the experimental group was significantly lower at each time point (P<0.05). Total and serially measured (4h, 24h, 48h, 72h) postoperative opioid consumption from 0 to 72h postop while lower in the experimental group, was only significant at 4h post-op (0.7 vs. 1.3; P=0.004).⁶² The main limitations of this study are a failure to use standardized adjuvant pain medications. No information regarding moving needle technique was provided but multiple sites were infiltrated. Similar rescue medication consisting of 5mg oxycodone/325mg acetaminophen was used. This study acknowledges the potential benefit of LB and notes room for improvement of MMA and control to optimize future studies.

The prospect of LB has been most widely attempted in total knee arthroplasty (TKA) patients with varying control groups. An initial RCT study done by Surdam et al in 2015 compared periarticular injection of LB (266mg/20ml in 40ml NS) against femoral nerve block (FNB). There was no significant difference in the primary outcome, pain control ($P=0.07$), or total opioid consumption ($P=0.41$).⁶⁴ Of note, while the FNB group required significantly fewer opioids on POD 0, the reverse was seen on POD 1 with the LB group requiring less instead. In addition, the LB group saw a higher percentage of patients ambulating on POD 0 and had a shorter average length of stay (LOS) ($P=0.03$). Once again, the sample size ($N=80$) was rather small and limits the study. Patients were also not blinded, which presents a substantial possibility for reporting bias. A possible reason for lack of significance in primary outcomes may be the addition of sustained-release oxycodone prior to operation and immediately postoperatively, which may skew the analgesic effects of LB. Similar breakthrough oxycodone was available for rescue pain relief. In a more recent RCT done by Talmo et al, LB (266mg/20ml) admixed with 0.25% bupivacaine and placebo FNB was compared with FNB alone. A larger sample size ($N=373$) to sufficiently power the study was complemented by significant improvements by the LB group in postoperative pain scores at 12h and 24h post-op (3.24 vs. 3.84; $P=0.0027$ and 4.16 vs. 4.73; $P=0.001$).⁶³ However, there were no significant differences in adverse effects or complications, and in a 3 month post-op follow-up, the LB group reported significant differences in physical function on a Short Form-12 survey when compared to the FNB group (-23 vs. -27 respectively; $P=0.03$). While these two trials fail to report any major improvements in pain or opioid consumption, they do demonstrate non-inferior pain control with possible functional improvements when using LB as compared to the standard of care.

Most notable of the TKA trials has been the PILLAR study. This RCT was unique in comparing local infiltration analgesia technique with LB (266mg/20ml) and bupivacaine HCL 0.5% (20ml) expanded to 120ml with solely bupivacaine instead of FNB. It has been speculated that previous trials were unable to obtain larger significant improvements in pain score or reductions in opioid consumption because bupivacaine was not added to LB in order to bridge onset of analgesia. LB admixed with bupivacaine had significant differences in both coprimary outcomes of mean area under the curve (AUC) VAS pain scores (-26.88, P=0.0381) and mean total opioid consumption 0-48h postsurgery (-66.2mg, P=0.0048).³⁷ This study was sufficiently powered with an adequate sample size (N=140). The utilization of a standardized infiltration protocol that incorporates moving needle with frequent aspirations and standardized MMA regimen that was opioid sparing was key to eliminating many limitations of previous studies.

LB's efficacy has also been tested in total hip arthroplasty (THA). A retrospective cohort matched study (N=58) utilized similar bridging of analgesia by comparing LB (266mg/20ml) admixed with bupivacaine 0.25% + epinephrine (40ml) against bupivacaine alone. Morphine equivalent use within the first 24h was significantly less in the interventional group (P<0.05).⁶⁶ The LB group also had a significant shorter length of stay (1.93days vs. 2.47days; P<0.05). Given the retrospective nature of the study, a major limitation was the inability to standardize perioperative MMA. An additional review by Zhang et al analyzed four THA studies and 308 participants. Their findings show LB infiltration significantly reduced VAS pain scores (P<0.000) and postoperative morphine consumptions (P<0.001) throughout 48h.⁶⁵ Incidence of adverse effects such as nausea and vomiting were also significantly lower in LB groups (P=0.019), which may be attributed to the decreased use of opioids. While the authors concede

that quality of evidence may be low and the review is limited by using only 4 studies, the potential benefits outlined warrant assessment in prospective RCTs.

Despite the collective evidence demonstrating LB's potential role in perioperative MMA, there are some conflicting findings. Reviews done by Dasta et al. and Bergese et al. looked at over a combined total of 19 trials and report significant decreases in total postoperative opioid use and pain scores, which is supported by improvements in many secondary outcomes and a high quality evidence grade.^{53,68} On the contrary, alternative reviews have highlighted a lack of significant outcomes, but mainly incorporated studies with smaller sample size and discrepancies in the number of opioids used in MMA regimens.^{69,70}

D. Efficacy of EXPAREL amongst spine surgery

LB's efficacy in other surgeries highlights a need to determine its role in perioperative MMA for spinal surgery. There is limited literature analyzing LB's effect on adjunctive opioid consumption and pain relief. Given the novelty of using LB in spine surgery, an extensive search of multiple journal databases identified seven completed studies and one ongoing RCT.

Initial benefit of LB was found in a retrospective analysis study (N=42) done by Wang et al reviewing patients undergoing transforaminal interbody fusion (TLIF). Although the study did not directly compare LB against another local anesthetic or analgesia, it did look at an approach called Enhanced Recovery After Surgery (ERAS) that incorporated LB (266mg/20ml in 20ml NS) as a key component. Overall the main outcome was improvement in Oswestry Disability Index (ODI) scores from 40 ± 13 preoperatively to 17 ± 11 (P=0.0001).⁷¹ The authors further remarked that high diffusion of LB had a major impact on postoperative pain control. However, the ERAS approach utilized does involve minimally invasive surgery (MIS) and comprehensive postoperative therapy, which can be attributed as confounders to the benefit observed. A

relatively small sample size also limits the external validity of this study. Given that no significant adverse effects or severe complications were noted, these preliminary results with incorporation highlighted the potential for future studies to isolate the benefit of LB alone.

The next study to incorporate LB improved upon the trial set forth by Wang et al. A prospective cohort study with retrospective cohort comparison (N=57) looked at benefit of ERAS that incorporated LB (266mg/20ml in 10-20ml NS for 3-level fusions) admixed with bupivacaine HCL (20ml) against standard of care (no ERAS) in posterior 1 to 3 level lumbar fusion surgery. The ERAS with LB group reported significantly shorter LOS (2.9 days vs. 3.8 days; P=0.01), less adjunctive oxycodone-acetaminophen on POD 0 (408.0mg vs. 1094.7mg; P=0.0004) POD 1 (1320.0mg vs. 1708.4mg; P=0.04) and POD 3 (1500.1mg vs. 2105.4mg; P=0.03), and lower pain scores significant only on POD 1 (P=0.006).⁷² Once again, these observed improvements may be attributed to MIS or the daily postoperative visits by the ERAS team and thus require more specific trials. The use of a single center and lack of prospective randomization limits generalizability. Despite these limitations, the use of a formal placebo and recognized clinical outcomes helped demonstrate increased support for LB.

In another prospective cohort study with retrospective cohort comparison (N=80) done by Puffer et al, field block using LB (266mg/20ml) admixed with 0.5% bupivacaine (20ml) was compared with field block using placebo saline in single-level lumbar microdiscectomy surgery. The LB group had significantly decreased average length of time requiring IV narcotic pain medication (-10.3 hours; P<0.001) but no differences in VAS pain scores or morphine equivalent dose (MED) opioid amounts. Upon further subset analysis due to concern for confounding by subjects with chronic pain, it was reported that average length of time requiring IV narcotic pain medications remained significantly lower in the LB group (P<0.05) and VAS scores were shown

to be significantly decreased in the LB group then the placebo group (2.4 ± 0.5 vs. 3.7 ± 0.5 ; $P < 0.04$).⁷³ The lack of consistent difference in VAS or MED may be attributed to a MMA regimen that was noted by the authors to include scheduled IV ketorolac Q6h and 5 mg oxycodone/325mg acetaminophen Q4h PRN with IV hydromorphone as rescue opioid medication. Heavy reliance on opioids in MMA may obscure the true benefit of LB. Another notable remark is the change in significance of improvement in VAS upon excluding chronic pain subjects. Both are potential confounders and can be utilized in future exclusion criteria.

LB efficacy in TLIF surgery was revisited in a prospective cohort study done Kim et al. The trial used a retrospective control cohort and compared LB (266mg/20ml in 40ml NS) against non-liposomal bupivacaine or lidocaine local anesthetic. The LB group exhibited significantly lower mean AUC VAS pain scores 12h after surgery (15.0 ± 15.6 vs. 45.6 ± 21.1 ; $P = 0.003$) and 24h after surgery (37.6 ± 20.6 vs. 48.4 ± 24.9 ; $P = 0.05$) with complementary decreases in adjunctive narcotic use between 12h to 24h after surgery (16.0 ± 13.4 mg vs. 24.1 ± 19.7 mg; $P = 0.04$).⁷⁴ Secondary outcome such as length of stay was also significantly shorter in the LB group when compared to the non-LB group (3.1 ± 0.9 days vs. 4.3 ± 1.3 days; $P < 0.001$). This study is notable for using a standardized MMA regimen to reduce confounding and ensuring baseline characteristics had no significant difference in preoperative pain conditions. Major limitations include the retrospective comparison and use of a small sample size ($N = 74$). However, no significant differences in adverse effects or complications were observed between the two groups, which along with the outcomes noted suggests strong evidence for LB's role in perioperative MMA.

Despite the collective evidence in previous studies, a retrospective cohort-matched review by Grieff et al. did not produce consistent significance in their results. In this trial,

posterior cervical and lumbar spinal surgery cases were evaluated for efficacy of LB (266mg/20ml in 40ml NS) against bupivacaine HCL. While the LB group required almost half the morphine milligram equivalent (MME) (2.7 vs 5.7 MME; P=0.27 [cervical] and 7.1 vs 17.3 MME; P=0.3 [lumbar]) and IV rescue analgesic amounts when compared to the bupivacaine group (0.39 vs 1.0 MME; P=0.31 [cervical] and 0.37 vs. 1.0 MME; P=0.08 [lumbar]), these results were largely insignificant.⁷⁵ The study encompasses a wide array of surgical indications for inclusion into the study, which has historically not been the case in previous studies. Of note, the trial remarks that chronic opiate users trended towards higher opiate requirements in the bupivacaine group but this data also did not achieve significance. Major limitations include use of a single center, single surgeon, small sample size, and retrospective design. A possible flaw in the study design may be preoperative PCA usage which could obscure the traditional MMA regimen that uses limited opioids in order to produce an optimal effect from LB. Ultimately the lack of significant results conflicts with previous trials, but offers opportunity for more specific RCTs that incorporate these limitations to evaluate LB's role.

Of the limited studies found, two RCTs were identified. Conducted by Chang et al. in 2016, the first RCT compared LB admixed with bupivacaine with bupivacaine alone in an adult population (N=68) undergoing elective lumbar fusion surgery with at least 7 levels involved. The LB group had markedly lower consumption of postoperative opioids with the greatest difference on POD 1, but no significance margin is specified (Day 0: 19.35 vs 28.76 MEU, Day 1: 74.85 vs 98.74, Day 2: 95.21 vs 102.82, Day 3: 87.29 vs 93.08).⁷⁶ Despite those changes, hospital LOS and pain scores were similar. Both groups had equal post-op complication rates (LB: 3[7.9%] vs C: 2[6.7%]). The specific surgical indication for inclusion into the study most likely comes after several studies in other surgical specialties highlight a role for LB in surgeries with extensive

dissection such as a 7-level fusion. An in-depth search revealed no other full text for this RCT, but the information provided substantiate the potential role for LB in perioperative MMA.

A more recent RCT done in 2018 by Brown et al. compared LB (266mg/20ml in 40ml NS) to saline injection in posterior lumbar decompression and fusion (PLDF) surgeries. Primary outcome of total 72-hour postoperative opioid consumption was slightly lower in the LB group but not significant (11.6 vs. 13.4 MME; P=0.4).⁷⁷ Secondary outcomes consisting of VAS and hospital LOS also saw no significant differences. Of note, narcotic tolerant patients did require significant more opioids than narcotic naïve patients (16.5 vs 9.9 MME; P=0.03), which may suggest a role for LB in specific instances of treating chronic opioid patients. The single surgical indication of degenerative spondylosis severely limits the extent of operations and range of surgeries that could have benefited from LB injection. Additionally, the single surgical indication affects the small sample size utilized (N= 50). Other major limitations include the lack of blinding of amongst research staff and investigators, which can introduce observe bias, and lack of standardized MMA, which has been shown by previous trials to skew analgesic effects of LB.

The inconsistency in data and lack of additional RCT that engage a broader range of surgical indications for lumbar fusion highlights room for improvement. Currently, a single RCT by Alcalá-Marquez et al. comparing LB to bupivacaine is in active recruitment, but it maintains limitations such as a small sample size, single surgical indication of degenerative spondylolisthesis, and primary outcome of pain scores and not adjunctive opioid consumption.

2.5 Review of Relevant Study Methodology

A. Study design

A review of the empirical studies above reveals a majority with prospective cohort retrospective controlled study designs and a lack of RCTs. A single RCT takes into consideration

the inconsistent results from prior literature but ultimately fails to demonstrate any significant improvement in postoperative opioid consumption or pain scores.⁷⁷ The collective evidence offers possibility for additional and more comprehensive randomized clinical trials that can improve on the limitations expressed by the study conducted by Brown et al.

We plan to conduct a prospective RCT. Further details of our study design include a multi-center approach and double blinding of both clinical investigators who record outcomes and patients. Prior studies have mainly used a single center^{60,72,74,77} and/or single surgeon approach,^{71,73,76} which hopes to maintain consistency in surgical technique and patient demographics. However, with a standardized treatment technique, injection of the intervention, and specific training of research staff, we hope to expand the generalizability and sample size of this study through the multi-center approach. Furthermore, the only apparent RCT done by Brown et al. failed to utilize double blinding, which introduces substantial reporting bias.⁷⁷ As a result, this played heavily into design of our study and incorporation of a double-blind approach.

B. Primary and secondary outcomes

Historically pain scores or postoperative opioid consumption have been used to assess pain intensity after surgery.⁷⁸ Visual analog scale (VAS) scoring has commonly been used and is recognized as a reliable standard. Many previous non-spine surgery studies reviewed opted for VAS scores as their primary outcome with opioid consumption following as a secondary outcome.^{61-64,66} However, amongst spine surgery studies, opioid consumption is frequently the primary outcome or co-primary outcome with pain scores.⁷²⁻⁷⁵ This may be in part due to the complementary relationship and expected simultaneous reduction between pain and opioid use. Therefore, our study aims to use postoperative opioid consumption as the primary outcome with VAS pain scores as a secondary outcome. Area under the curve (AUC) analysis of VAS pain

scores has previously been used by Kim et al., and is an important tool to calculate total pain scores as a product of time.⁷⁴

The intent to measure from 0 to 72 hours post-surgery with either 12h or 24h measurements has been used in prior studies and is a means of establishing a more standardized measurement of opioid consumption amongst all subjects.^{61,62,64,66,72,74,76} Other studies have recorded opioid use through discharge or POD 30,^{59,60} which can skew results as subjects that have a longer length of stay will undoubtedly consume more opioids as a product of time. As a compromise, a secondary outcome of total opioid consumption at 14 days will be used to note any delayed improvement from LB. Additional outcomes such as # of opioid adverse effects through 14 days will be recorded to re-confirm safety.

C. Study population and recruitment approaches

The study population will enroll adults that have a surgical indication for undergoing elective postoperative lumbar spine fusion. A review of prior spine surgery studies shows use of a narrow list or often single surgical indication(s) when enrolling subjects, which may limit the generalizability of the results.^{71,77} The use of a single surgical indication as shown by Brown et al. may obscure the range of potential benefit from LB. While we could use a single specific indication to create more internal validity, it is not pragmatic as there are a plethora of conditions that can be surgically treated by spine fusion. Following the other previous spine studies that have wide indications,^{72,75} Therefore, we plan to diversify the list of indications that will allow enrollment into our study. These include spinal stenosis, spondylolisthesis, radiculopathy or unstable disc disorders, and degenerative disc disease. Recruitment will be expanded as well. Previous non-spine surgery and spine surgery studies often restrict their cohorts to single

centers.^{72,74,75,77} Use of multiple spine surgery institutions encompasses a wider sample population, which adds to external validity.

D. Inclusion and exclusion criteria

Inclusion criteria were established based on prior spine surgery studies. With the exception of a widened range of surgical indications eligible for inclusion into the trial, most of the inclusion criteria is consistent with general standards used in the reviewed spine studies.^{71-75,77} This includes but is not limited to age within 18 to 75 years old, non-pregnant to in order to avoid harm to a fetus, cognitively intact in order to provide informed consent, and undergoing elective open lumbar posterior spine fusion. More specifically, the lack of significant difference in pain scores observed in the study by Puffer et al. where only single-level fusion was utilized, reflects the known difference in pain associated with single vs. two-level fusions.⁷³ Therefore, our study will only include two-level spine fusions. Furthermore, the decision to not include fusions of three or more levels is due to the added traumatic nature of the surgery, which contributes to iatrogenic rigidity or new back pain and is reflected by the lack of significant changes in pain scores when patients had at least 7-level fusions.⁷⁶ The decision to focus on solely two-level fusions will reduce variability in our study.

Exclusion criteria was created based on prior spine surgery studies reviewed as well.^{71-75,77} There is a primary emphasis on reducing possible confounders or secondary medical conditions that may be exacerbated by the trial. These include significant spinal pathology that may influence surgery technique, any allergies to trial medications, prior spine surgery, severely low or high BMI, and poor surgical procedure. The main addition to the exclusion criteria comes after reviewing the study done by Puffer et al. and Brown et al where chronic pain conditions were shown to skew results or demonstrate improved benefit respectively.^{73,77} As a result, history

of opioid or alternative drug abuse, high presurgical opioid use, and recent opioid use within 3 days of screening will prevent participation in the trial.

E. Intervention

Delivery of local anesthetic will be given through local infiltration analgesia as demonstrated in previous trials.^{73,74,77} This is a known technique for delivering local anesthetics intraoperatively prior to wound closure. Currently the approved max dosage of liposomal bupivacaine is 266mg/20ml or 1.3% LB. Prior studies have shown this is the most efficient dosage as it maintains sensory blockade with reduced motor blockade than other local anesthetics.^{53,54} Among the studies reviewed, many dilute the initial 20ml of 266mg LB in normal saline as a means of expanding the volume for dispersed distribution.^{59-62,64,71,72,74,75,77} Most notable is the PILLAR trial which expanded the total volume to 120ml for distribution over the entire knee capsule and reported significant results.³⁷ As per guidelines from Pacira Pharmaceuticals, 120ml is an acceptable final volume given the large surface area and surgical field that will be operated on in lumbar spine fusion. The final addition to the intervention will be admixing LB with bupivacaine. This has been prominent in other surgical fields with significant results^{37,62,63,66} and in two of the spine surgery cohort studies,^{72,73} but has only been used in one of two spine surgery RCTs reviewed.⁷⁶ Admixing has been shown to bridge analgesia due to delayed release of LB.

F. Multi-modal analgesia (MMA) and adjunctive opioid rescue regimens

The importance of incorporating perioperative multi-modal analgesia is well established.^{38,41,79} Yoo et al. and Bhatia et al. have established fairly extensive MMA protocols for spine surgery with specific medications for preoperative, intraoperative, and postoperative periods.^{38,79} However, there exists reliance on preoperative and postoperative non-rescue opioid

incorporation. Among the clinical studies reviewed, those with perioperative MMA that restricted regular opioid use had more significant outcomes^{37,59,60,74} while those that provided preoperative and postoperative opioids were often reported reductions in pain or adjunctive opioid use that lacked statistical significance.^{64,73,75,77} Therefore, the perioperative MMA used in this study will restrict opioids and include medications associated with conventional MMA that have established efficacy such as NSAIDS, acetaminophen, gabapentinoids. Adjunctive or rescue opioid provided will consist of PO oxycodone or IV hydromorphone. This was selected for based on the standard set by prior studies.^{37,59,60,62}

G. Confounders

Previous reviews on postoperative adjunctive opioid use and pain across all surgery have reported several notable confounders. Overall, younger age, history of psychological distress including anxiety, depression, or abnormal mood, and extent of preoperative pain are correlated with poor pain control, increased postoperative analgesic consumption, and higher pain intensity scores.^{80,81} Of note, there is conflicting results between two reviews regarding the importance of pain catastrophizing and pain tolerance as one demonstrated significance of these variables on impacting postoperative pain results⁸⁰ and the other showed lack of correlation.⁸¹ Female sex has been demonstrated to be a predominant indicator for worst postoperative pain,⁸¹ especially amongst orthopedic procedures. However, a study by Zheng et al reports that age and preoperative pain are specific sub-factors that influence this difference observed between sexes.⁸²

More specifically in spine surgery, baseline preoperative back pain has shown significant correlation with predicting increased postoperative pain intensity scores.^{73,83-85} The utility of establishing a baseline preoperative pain level with VAS and ODI pain questionnaires was shown by Rungwattanakit et al. This study marks the potential for using preoperative pain

assessments in doing subset analysis on postoperative pain scores and opioid consumption given that the evidence isn't compelling enough to warrant stratification of the subjects. Individual pain sensitivity has also been shown to predict extent of postoperative pain following lumbar spinal surgery^{77,85} Brown et al being the only current RCT regarding LB's role in spine surgery established that subjects' comorbidities may influence adjunctive opioid consumption.⁷⁷

Despite the significance of the factors mentioned above and reviewed in prior studies in displaying correlations with increased postoperative pain intensity or adjunctive opioid usage, there is no overwhelming evidence regarding a single confounding factor found upon review of empirical studies. None of the above potential confounders has demonstrated a strong role in the reviewed research to suggest they could skew results. Given the large sample size and conservative effect size used to calculate it, randomization should be sufficient in dispersion of subjects with confounding variables to both the experimental and control groups.

H. Sample size

Many of the reviewed trials have consistently reported small sample size as a severe limitation of their study.^{59,60,64,71,74,75,77} This in turn reflects studies that have poor internal validity. Therefore, one of the staple elements of this clinical trial is enrolling a sufficient number of subjects in order to appropriately power the study. To do this properly, we decided to review prior studies as a means of calculating a relative effect size that could be used to determine an adequate sample size. A series of studies involving bupivacaine as the local anesthetic of choice for the control group^{74,86-90} were reviewed to ascertain a baseline for morphine equivalent doses (MED) that is to be expected at 72h post-surgery. Subsequently, a series of studies involving LB as the intervention and bupivacaine or placebo as the control^{37,53,66,68} were reviewed to determine the average difference in MED at 72h post-surgery.

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Chapter 3: Study Methods

3.1 Study Design

We will conduct the proposed study as a prospective, multicenter, two armed, randomized, double-blinded, controlled, parallel group (standard of care local infiltrative analgesia-controlled) clinical trial among adult male and non-pregnant female subjects undergoing elective open lumbar posterolateral spine fusion. A centralized verified computer system will be used to randomize study subjects to the treatment or control. The computer software will generate random subject codes and communicate these to the study sites. Each subject will be assigned a unique subject identifier and unique random code identifier. Both study personnel and subjects will be blinded to treatment throughout the study period to reduce reporting and observational bias respectively.

3.2 Study Populations and Sampling

The source population will be derived from men and non-pregnant women between the ages of 18 and 75 undergoing elective open lumbar posterolateral spine fusion with an indication for surgical correction. Eligible subjects who meet inclusion criteria but no exclusion criteria (Table 1 in appendix) and have given consent, confirmed by participating surgeons, will be enrolled consecutively as they present. Exclusion based on primary language spoken will not be utilized due to the need to maximize recruitment for effective sample size. On site hospital interpreters will be utilized when possible to clearly communicate all the information regarding the trial, eligibility, participation, and assessment of outcomes.

A preoperative screening visit will be scheduled < 30 days and >1 day prior to surgery in order to evaluate the eligibility of the subject. A questionnaire will be included to assess physical activity. Physical exam will be done to detect any comorbid diseases. Vital signs measurement,

urine drug screen, alcohol breath test, pregnancy testing, and comprehensive metabolic panel/complete blood count blood tests will be drawn.

3.3 Subject protection and Confidentiality

Prior to the start date of recruitment, the study proposal will be submitted for review and approval by the Institutional Review Board (IRB) at each of the enlisted study sites prior to study commencement. A detailed report consisting of the proposed clinical intervention, funding resources, prospective research team requirements, training modules for participating providers and research assistants, and patient confidentiality measures will be included for evaluation.

In order to satisfy eligibility requirements and participate in the study, all study subjects will be required to sign a written informed consent form (ICF) that will be available in multiple languages. Interpretation assistance will be provided in order to facilitate informed consent when the study subject signs the form. Study subjects will concurrently receive a copy for their own record. Informed consent forms will include the study description, total duration of participation, potential risks and benefits of participation in the study, and alternative options for treatment of the surgical indication requiring either of the two treatment arms. In addition, the consent form will confirm that subject participation is voluntary and that by signing the form or enrolling in the study, the subject authorizes research personnel to access a subject's protected health information (PHI). Due to the nature of sensitive PHI being transferred between study subjects and personnel, all research members involved with the study will be required to successfully complete Health Insurance Portability and Accountability Act (HIPAA) training.

In order to maintain subject confidentiality, the study protocol will adhere to HIPAA. As mentioned above, all study subjects will be assigned a unique subject code identifier that will be used to label all data related to that patient. As a means of reducing collection of unnecessary

patient information, collection of subject health information will be restricted to pertinent data that may meaningfully influence the outcomes or analysis of outcomes. All patient information will be stored on an encrypted secure server that can only be accessible by authorized research personnel involved with the research study.

3.4 Procedures and Recruitment

In order to satisfy the inclusion criteria of patients undergoing elective two-level lumbar fusion surgery and enroll a sufficient number of subjects to adequately power the study, orthopedic institutes of eligible hospitals across the US will be approached in order of their surgery incidence ranked from greatest to lowest as a means of satisfying the required sample size estimated. A letter describing the study will be distributed to service chiefs in the orthopedic service lines at each respective hospital site. Participating providers will be enlisted for their help in recruiting eligible subjects for the study. Recruiters will screen all patients getting scheduled for elective posterior lumbar surgery. Once eligibility is confirmed, patients will be approached by the site recruiter and informed of the study guidelines, eligibility, and medical implication of the investigation. Patients will be informed that study participation is strictly voluntary and prohibited if any exclusion criteria are discovered. Upon patient agreement, signed, written, and informed consent will be obtained. No compensation will be given for participation in the study.

3.5 Study Variables and Measures

Independent Variable: The independent variable is the treatment arm to which the patient is assigned: Liposomal bupivacaine (brand EXPAREL) admixed with plain bupivacaine or standard of care. Both groups will receive their respective local anesthetic through an intraoperative local infiltrative analgesic approach. *Primary Dependent Variables:* The primary efficacy endpoint consists of mean total adjunctive opioid rescue, measured in mg Morphine

equivalent dose (MED) PO from 0 to 72 hours after surgery. *Secondary Dependent Variables:*

The secondary efficacy outcomes consist of total adjunctive opioid consumption in mg MED PO at 14 days after surgery, time to first opioid rescue through 72 hours or discharge, number of opioid related adverse events assessed by using Opioid Related Symptoms Distress Scale (OR-SDS) at 24h/48h/72h/through discharge/14 days post-surgery, and area under the curve (AUC) of postoperative visual analog scale (VAS) pain intensity scores at rest collected post surgically at 4h/12h/24h/48h/72h/through discharge. *Additional Dependent Variables:* Health outcomes consists of total length of stay, discharge readiness, discharge disposition, 30 days all cause readmissions, 30 days readmissions related to pain, 14 days office visits or calls to doctor related to pain, and total time spent in PACU or step-down unit. *Other Descriptive variables:* Study subject characteristics (Table 2 in appendix) will be used to assess the quality of randomization and determine any potential confounding variables within our study.

3.6 Methodological Considerations

A. Description of intervention, control, and follow-up

The intervention treatment arm is liposomal bupivacaine (brand EXPAREL) 266mg/20ml (1.3% undiluted drug) admixed with bupivacaine HCL 0.5% 20ml and expanded to a total volume of 120ml with saline that will be given in the intraoperative setting via standardized local infiltrative analgesic technique.

The control treatment arm is the standard of care local anesthetic or standalone bupivacaine HCL 0.5% 20ml and expanded to a total volume of 120ml with saline that will be given in the intraoperative setting via standardized local infiltrative analgesic technique.

Follow-up will be carried out by dedicated research assistants blinded to the treatment received by each subject. Follow-up will be carried out in 3 portions: inpatient, postoperative day

14, and postoperative day 30. Inpatient assessments will be carried out at the bedside. Post-discharge assessments will be carried out by phone calls to the study subjects.

B. Experimental protocol

The study will span a maximum duration of 63 days per subject. Once study subjects are confirmed eligible for participation within the 30-day screening period prior to day of surgery, specific protocol for multimodal analgesia must be followed. All participating providers will perform surgeries based on their usual surgical technique. The protocol is as follows:

Handling of EXPAREL: EXPAREL is provided in single-use, clear glass vials. Vials should be stored in refrigerators between 2°C to 8°C (36°F to 46°F). Upon withdrawing EXPAREL from its vial into a syringe, it may be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration. Given specific storage requirements, avoid usage of vials with bulging stoppers, that have been re-refrigerated after 1 month of storage at room temperature, or suspected of exposure to extreme temperatures.

Usage of EXPAREL: DepoFoam particles within the EXPAREL formulation are denser than the diluent and tend to settle with prolonged rest. Therefore, prior to drawing up EXPAREL, the vial should be inverted multiple times in order to re-suspend the particles immediately before withdrawal into a syringe. It is paramount that you do not shake the vial. All vials lack any antimicrobial preservatives so any unused portions should be discarded. EXPAREL should be injected slowly (generally 1 to 2 ml per injection) with frequent aspiration to check for blood and to minimize risk of inadvertent intravascular injection.

Infiltration technique: Given a total volume of 120ml for both treatment arms, both the intervention and control will be administered using six 20-ml syringes with 22-gauge needles to deliver a total of 120ml of drug prior to wound closure. Infiltration will target the thoracolumbar

fascia and subcutaneous fat layers. Each injection will occur in a direction that is perpendicular to dermatomal innervation. Approximately 1 to 1.5 ml of drug will be administered with each needle stick with visualization of tissue expansion to ensure minimal drug leakage from intended areas. All local infiltration analgesia will be given by the attending surgeon conducting the elective surgery and follow the standardized procedure as outlined above.

Pre-operative medications (within 24-48 hours prior to surgery) will be limited to Tylenol (acetaminophen) 1000mg PO, Gabapentin 300mg PO, or Robaxin 750mg PO. There will be a restriction on bupivacaine or any other local anesthetics within 7 days of screening, long acting opioid medications (hydromorphone or oxycodone) for more than 3 months or within 3 days pre-op, NSAIDs/aspirin/acetaminophen within 3 days pre-op, Dexmedetomidine HCL within 3 days pre-op, neuropathic pain meds (SSRIs/SNRIs/gabapentin/pregabalin/duloxetine) within 1 month of surgery day, use of an investigational drug within 30 days or 5 elimination half-lives of drug, or planned administration of another investigational product during subject participation.

Intra-operative medications besides the intervention and control treatment will be limited to Propofol for induction, Fentanyl for short-acting analogues, or any medication for nausea, vomiting, and pruritus prevention at the participating surgeon's discretion. There will be a restriction on the admixing of any other drugs with the study drug other than bupivacaine HCL, on contact between EXPAREL and any topical antiseptic (area must be dry prior to administration of EXPAREL), use of any long-acting opioids (morphine, hydromorphone) /acetaminophen/ketorolac/NSAIDS unless for adverse effect, and use of any additional local anesthetic within 96 hours following administration of EXPAREL.

Post-operative medications will be a standardized multi modal pain regimen consisting of Tylenol (acetaminophen) 1000mg PO TID with a limit of 3000mg daily (IV formulation to be

used if PO is not tolerated), Gabapentin 300mg PO BID or Pregabalin 150mg PO BID, and Robaxin 750mg BID or TID. There will be a restriction on any other analgesics not mentioned above within 72 hours after EXPAREL administration or discharge from the hospital and any local anesthetics within the “-caine” family through 96 hours following EXPAREL administration due to possibility of interference with pharmacokinetic profile of bupivacaine.

Post-operative adjunctive opioid medications will consist of a standardized format starting with immediate-release oxycodone < 10mg PO Q6h or PRN. If subject is unable to tolerate oral medications, morphine 2.5 – 5mg IV or hydromorphone 0.5 – 1mg IV Q6h or PRN can be given. All other analgesics not mentioned above will be restricted in order to maintain consistency in opioids delivered amongst all subjects.

C. Randomization procedure and assignment of intervention

After confirming eligibility for study participation, each study subject will be initially de-identified for confidentiality by verified computer software. The computer system will generate a unique subject identifier code that will be conferred on all PHI related to that unique study subject. Upon assigning an identifier code, the computer system will randomly assign an intervention. This will be denoted in a concealed envelope handled by a single un-blinded research assistant with the duty of preparing the local anesthetic to be injected intraoperatively.

D. Blinding

Study subjects will be blinded to their treatment. However, due to the turbulent nature of the liposomal suspension, participating providers cannot be blinded to the treatment arm being used during surgery. The use of a syringe that obscures the contents also cannot be utilized due to the need for the operating provider to be able to visualize any blood return upon drawing back

on the syringe when assessing for vascular infiltration. Research personnel assessing outcomes and recording data will be blinded to the treatment received by subjects.

E. Adherence

Intervention or control local anesthetic will be administered during the surgery by participating providers. Therefore, adherence to the intervention or control treatment arms will be strictly controlled. In addition, the length of exposure time to the independent variable should encompass no more than a couple minutes for injection, which should provide almost null possibility for non-adherence to the intervention or control. Adherence to reporting of health outcomes and opioid use post discharge will heavily rely on proper follow up phone calls and visits, as needed, at 14 days and 30 days post-surgery.

F. Data collection

Initial screening assessment will be carried out no more than 30 days prior to day of surgery. The data collection will be obtained by interview, questionnaire, and providing of samples for clinical testing. During initial screening, collection of baseline data and determination of comorbidities will be procured. Subjects will provide ICF, medical/surgical history, and prior or concomitant medications. Subjects will record a baseline pain intensity score, opioid use history, Brief Pain Inventory-short form (BPI-sf), Hospital Anxiety and Depression Scale (HADS), Survey of Pain Attitudes (SOPA), and 5 item Opioid Compliance Checklist. In addition, study subjects will participate in a vitals measurement (including height/weight/BMI) and a urine pregnancy test.

Initial inpatient follow-up assessments will begin on day of surgery (day 1 of study). Data collection will be obtained by interview and questionnaire. Data will consist of recording duration of surgery, PACU arrival and departure date/time, recording of time and dose of all pain

management medications administered, and continued monitoring of adverse effects. Inpatient follow-up assessments will be carried out through discharge, which will consist of the recording of pain intensity score at 6h/12h/18h/24h/30h/36h/42h/48h/72h/through discharge and completion of BPI-sf, OR-SDS, and discharge readiness questionnaires at 24h/48h/72h/through discharge.

Upon discharge, two subsequent follow-up assessments will be performed and carried out by phone calls scheduled for Day 14 \pm 1 and Day 30 \pm 3. The same dedicated research personnel that followed each subject while they were hospitalized will conduct these phone calls. Data collection will be obtained by phone interview and questionnaire. The post-discharge assessment at Day 14 \pm 1 will be comprised of a pain intensity score, BPI-sf, OR-SDS, documentation of any phone calls or office visits related to or unrelated to post-discharge pain, documentation of any requests for refills of opioid medication, recording of any adverse effects or complications, and recording of date and time of all opioid/non-opioid rescue medication use. The post-discharge assessment at Day 30 \pm 3 will be comprised of determination of any persistent opioid use, documentation of any hospital readmissions for pain or any cause, documentation of unscheduled ER visits related to pain, and recording of any adverse effects or complications.

G. Sample size calculation and site recruitment

Sample size was computed using Power and Precision Version 4.0 software and calculated via an algorithm comparing means of two independent samples by t-test. Given the novelty of this study, there have been few studies that compare EXPAREL and bupivacaine in a sample population undergoing spine surgery with a primary outcome of 0 – 72h postoperative adjunctive opioid consumption. Therefore, our sample size calculation is based on a relative effect size determined from prior studies. The first set of studies consisted of those that used

bupivacaine control in a sample population undergoing spine surgery with postoperative adjunctive opioid consumption recorded at 24/48/72h intervals in order to calculate an average postoperative adjunctive opioid consumption amount for our control arm. Afterwards, a second set of studies consisting of those that tested EXPAREL against bupivacaine control across multiple surgical specialties was used to determine an average decrease in adjunctive opioid consumption expected from EXPAREL. From those sets of data, a baseline of 93.3 ± 62.7 mg adjunctive opiates can be expected in the control arm and a mean between-group difference of 27.67mg in adjunctive opioid consumption was the determined effect of EXPAREL. Together, this represents a relative effect size of 29.65%. However, due to the heterogenous nature of the data associated with EXPAREL and novelty of the proposed study, our study will aim to detect a 18.66 (mg IV morphine equivalent) between-group difference in geometric means or 20% relative effect for total adjunctive opioid dose. Our study will assume an 80% power ($\beta = 0.20$) and 2-sided t test with $\alpha = 0.05$. In sum, this calculates (see appendix for copy of program calculation) a required sample size of 179 per treatment arm. Adjusted for 10% expected drop-out rate and ensuring an even number of participants for balanced randomization, a total of 199 per treatment arm is the required goal.

H. Statistical analysis

Initial analysis of baseline characteristics and outcomes will be done using statistical tests prior to subsequent statistical analysis using the aid of computer software. Descriptive statistics, primary outcomes, secondary outcomes, and additional health outcomes as mentioned above are listed below with their respective appropriate statistical analysis (Table 3, 4, 5, and 6 in appendix). Categorical variables being recorded as proportions (%) and continuous variables being recorded as means (\pm SD). Statistical tests performed will include a 2-tailed Chisquare test

for proportional differences in dichotomous variables and a 2-tailed independent Student *t* test for the means \pm standard deviation of normally distributed continuous variables. One exception will be made for the secondary outcome of time to first opioid rescue through 72h or discharge, which will be analyzed by Kaplan-Meier analysis. Nonparametric data for continuous variables will be compared instead using the Wilcoxon rank sum test. An alpha error of 5% ($P \leq 0.05$) will be set as the threshold for statistical significance for all tests.

I. Timeline, personnel, and location

The study period will be 2 years including recruitment and protocol completion. Pending prior IRB and HIC approval, enrollment will commence on July 31, 2020 and continue on a rolling basis until May 29, 2021 given that the maximum duration of study participation is 63 days: screening period and study period are each 30 days, with 3 days variability in procurement of post-discharge follow up assessment at postoperative day 30. Subjects will be scheduled for the study protocol once screened for eligibility and enrolled randomly into an experimental cohort or control group. Protocol completion or study period for each individual subject will span 30 days with day 0 being the day of surgery and day 30 ± 3 being the final post-discharge follow up assessment. The study requires 2 primary overseeing principle investigators. Assigned to each study site will be 2 research assistants tasked with recording outcomes and characteristic data. Participating providers/surgeons, ideally 2 at each study site, will be tasked with screening potential eligible study subjects and delivering the intervention or control treatments. The study will be headquartered at the Yale Spine Center and overseen by the primary investigator and co-primary investigator.

Chapter 4: Conclusion

4.1 Strengths and Advantages

The foremost strength of this study is that it will be one of the few prospective RCTs done to study the effects of LB against conventional local anesthetic in lumbar posterior fusion spine surgery, a study population that is increasingly growing due to the large incidence of chronic low back pain. This study takes advantage of the limitations presented in prior literature and improves upon them in order to demonstrate a clearer effect of LB.

Admixing of liposomal bupivacaine with bupivacaine is both an advantage and possible limitation to be addressed in the section below. The strength of using a mixed formulation allows ethical coverage of the initial 24h of acute postoperative pain following spine surgery and has demonstrated success in previous TKA¹ and THA studies.² If postoperative adjunctive opioid consumption is not significantly different between experimental and control groups in the initial 24h, this merely reflects noninferior or lack of contribution by EXPAREL. However, in the event that the experimental group does experience slight improvement or significant decreases in the primary outcome, such a relationship can reflect a possible positive contribution by EXPAREL when added on top of the standard bupivacaine within the initial 24h in the experimental group.

In addition, the strength of the study lies in its very specific and feasible design. The variable of postoperative adjunctive opioid consumption being measured is attainable and specific to the problem being addressed, which is a need to demonstrate a role for EXPAREL in MMA in order to reduce dependence on opiates. Expanding the inclusion criteria to allow multiple spinal degenerative conditions as surgical indications also increases the range of our generalizability compared to prior studies that focused on a single indication. By doing a proper review of prior studies to determine a more relative effect size of LB on opioid use, a more

accurate sample size could be calculated. Concurrently, the larger sample size reflects adequate powering of the study, which is a major strength when compared to prior studies that were often small and underpowered. The diverse and larger sample size more directly reflects the study population undergoing lumbar fusion surgery. Incorporation of multiple study centers allows for an expanded patient population that will reduce any statistically significant differences in baseline characteristics between experimental and control groups. Furthermore, the 63-day timeframe, which affords extra time for pre-surgical screening, is reasonable and allows for incorporation of a sufficient number of subjects.

4.2 Limitations and Disadvantages

With any surgical study, there will inherently exist a limitation in the ability to standardize the surgical procedure utilized. There is a possibility to design the study with the intention of having a single surgeon conduct all surgeries in order to reduce confounding and to control for another possible variable that may influence outcomes. However, such a design may be limited by the number of subjects that a single surgeon can treat and the amount required to sufficiently power the study. Additionally, while a surgeon can practice a fairly uniform surgical technique, each patients' anatomy and developments of the surgery can create variable instances where different techniques are utilized to achieve the same outcome of the surgery, ultimately resulting in possible confounding. Therefore, this limitation is sacrificed to sufficiently power the study with the belief that an adequate sample size and comparison of baseline characteristics amongst surgeries can rule out any confounding from surgical technique.

The second major limitation of this study is common amongst all pain relief trials, and it is the inability to control for variability in patients' pain thresholds as a source for confounding. Fundamentally, pain experienced is correlated with amount of opioid rescue requested in order to

alleviate that situation. However, literature has shown that pain is extremely subjective and can affect in tolerability amongst people.³ It can be suggested to stratify based on subjects' baseline pain threshold but ultimately inflicting pain without a clinical purpose would be an unethical situation. Despite this possible confounder, the randomization and incorporation of an adequate sample size should be able to balance any variability in baseline pain threshold.

The last known disadvantage of this study is the inability to utilize an experimental group that uses EXPAREL as the sole intervention. In order to maintain the ethical standards of this study, EXPAREL cannot be the sole intervention as demonstrated in prior literature due to its delayed onset of activation. This would result in poor and inadequate postoperative pain management in the early stage of acute postoperative pain (0-24h) and render subjects with pain out of proportion. Therefore, EXPAREL is admixed with standard of care bupivacaine HCL or conventional local anesthetic to cover the initial 24h until the liposomal encapsulation begins to degrade. Despite this disadvantage, it is presumed that while bupivacaine's coverage of postoperative pain should subside shortly after 24h, the delayed activation of EXPAREL will convey longer postoperative pain management to cover the remainder of the acute postoperative pain period of 72h and ultimately reduce the primary outcome total opioid consumption.

4.3 Clinical Significance

The prevalence of postoperative pain is high with more cases being associated with spinal surgery. With new minimally invasive operations, more trained surgeons, and improving surgical techniques, the incidence of postsurgical pain is projected to increase. While acute postsurgical pain is transient and usually subsides within 3 days with adequate pain management, it has been shown that inadequately managed pain can lead to chronic morbidity including chronic pain,⁴ delayed return to normal gait, and restricted range of motion. The current standard of care is a

multi-modal analgesic treatment plan that has shown efficacy but requires improvement due to its reliance on narcotic opioids. Therefore, this study's significance is in redefining local anesthetic's role in MMA by addressing the limiting factor of short duration of drug action. The development of a role for LB in perioperative MMA for spinal surgery will offer a more reliable and effective means of pain relief that concurrently aims to reduce patients' dependence on opiate therapies.

With regard to the PA profession, the nature of SDD and its association with LBP is extremely relevant. PAs practice in a variety of sub-specialties, of which primary care and orthopedic surgery are included. Patients with back pain stemming from degeneration are 10% more likely to visit their primary care initially before seeing any orthopedic.⁵ By developing a role for EXPAREL in MMA for reducing postoperative pain and improving the outcome of spine fusion, PAs working in primary care will gain knowledge of a more efficacious treatment that they can recommend if their assessment of patients' back pain warrants a surgical approach. In addition, PAs working in the orthopedic surgery field will be able to utilize this approach in carrying out perioperative analgesic care for their patients. In the future, solidification of LB as safe and successful pain treatment can be utilized by the translational nature of PAs through various medical specialties that also present with patients in acute postoperative pain.

4.4 Summary

This is a novel study that aims to determine a role for LB in perioperative MMA for management of postoperative pain to improve spine surgery recovery through a prospective RCT. Utilization of multiple spine centers and focus on posterior lumbar spine fusion ensures a fairly abundant study population to select from with a feasible study period. Patients are undergoing an elective surgery and are not withheld from a potentially lifesaving therapy.

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Appendices

IRB Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: EXPAREL compared to conventional local anesthetic for postoperative pain relief following spinal surgery

Principal Investigator: Dr. Peter Whang, MD

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to look at a liposomal bupivacaine's (brand EXPAREL) potential improvement of postoperative pain in adult patients undergoing posterior spinal surgery. You have been asked to participate because you are electing to undergo posterior lumbar spinal fusion due to an indication of spinal degeneration and you are 18 years or older. Approximately 266 persons will participate in the study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participating in this study, you will be randomly assigned to receive (a) liposomal bupivacaine admixed with bupivacaine to be given intraoperatively by local infiltration analgesia during spinal surgery after confirmed eligibility OR (b) bupivacaine to be given intraoperatively by local infiltration analgesia during spinal surgery after confirmed eligibility. Either way, you will be asked about postoperative pain levels and monitored for the number of adjunctive opioids you require for sufficient pain relief.

Regardless of which local anesthetic you are selected to receive, you will undergo an initial screening assessment no more than 30 days prior to the day of surgery, which will consist of an interview, questionnaire, blood draw, and collection of baseline data including current pain, anxiety, depression, attitude toward pain, and opioid use. Depending on which group you are randomized to, you will receive either liposomal bupivacaine admixed with bupivacaine (experimental group) or bupivacaine (control group) intraoperatively during your posterior

lumbar spinal fusion. Both groups will be subjected to the same surgical technique and infiltration of the local anesthetic.

Follow-up assessments will begin postoperatively on day of surgery and continue for 3 days or until discharge. The investigators will interview you and ask you to fill out questionnaires about your pain intensity, presence of any adverse effects, and discharge readiness. Upon discharge, two subsequent follow-up assessments will be performed and carried out by phone calls scheduled around Day 14 and Day 30 after your surgery. The same research personnel that conducted your interview in the hospital will conduct the phone call. The phone call will consist of a similar interview and questionnaire about your pain intensity, presence of any adverse effects, documentation of any phone calls or visits related or unrelated to post-discharge pain, and documentation of any refills for opioid medications. The questionnaire at Day 30 will also ask for any persistent opioid medication use, any hospital readmissions for pain or any cause, any unscheduled ER visits related to pain, and report of any adverse effects.

A description of this study is available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. (See *Clinical Trials Identifier Number* _____) This Web site will not include information that can identify you. The purpose of this database is to allow everyone to see information on what studies are being done, and what studies have been done. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. Research results will not be returned to your doctor. If research results are published, your name and other personal information will not be given.

Risks and Inconveniences

Liposomal bupivacaine has been studied in a number of clinical trials for use in perioperative multi-modal analgesia in many surgeries. There are low rates of commonly observed adverse effects associated with liposomal bupivacaine as reported by the manufacturer, which include tachycardia, pruritus, constipation, nausea, vomiting, dizziness, headache, somnolence, and fever. A major cause of adverse effects is high plasma levels, which may be due to over-dosage, rapid absorption, diminished tolerance, or slow metabolic degradation. Neurological or cardiovascular toxicity are side effects that require immediate treatment. Due to the slow degradation of the lipid encapsulation, there is a potential for local adverse effects.

There are potential risks of accidental intravascular injection because local infiltration analgesia involves needle injections of the local anesthetic into the wound site, but this risk will be mitigated by a moving needle technique with frequent aspiration. Given the incorporation of a new drug, there is a risk of medication interaction or allergic reaction to the drug due to naïve exposure.

We will also ask to have your blood drawn in the beginning of the study for initial screening assessment. The risks involved in drawing of blood from a vein may include, but are not limited to, temporary discomfort at the site of the blood draw, possible temporary bruising, redness, and

swelling around the site, bleeding at the site, feeling of lightheadedness during the blood draw, and rarely, an infection at the site of blood draw. Infection risk will be mitigated with antiseptic and sterile technique as possible.

Other risks from participating in the study include the breach of confidentiality about your health status and participation in the study. This is very unlikely to occur, as all study investigators are trained and certified in research privacy. There are no other major risks involved with the experimental drug.

Given the extensive follow up, there will be minor inconvenience to ascertain further information at 14 and 30 days after discharge to document secondary results of the study.

Benefits

There are potential benefits resulting from the study including decreased physical discomfort, improved quality of life, decreased postoperative pain, and reduced opioid consumption. This study may also provide better insights to EXPAREL's potential in perioperative MMA for opioid tolerant patients.

Economic Considerations

The experimental drug (EXPAREL) or control drug (conventional bupivacaine) will be provided to you free of charge as the standard of care for your elective spinal surgery includes local anesthetic analgesia. There are no other costs associated with your participation in the study.

Treatment Alternatives/Alternatives

If you choose not to participate in this study, there are alternative treatments available, including those that are already being administered by your physician including pharmacotherapy (medications/drugs), exercise plans, and psychological treatments. You may choose not to participate.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information

that might directly identify you, such as his or her name and address, telephone number, and email address, or mobile phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information, and this link will be kept secure and available only to the principal investigator or selected members of the research team. Any information that can identify you will remain confidential. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Research study records
- Records about phone calls made as part of this research
- Records about your study visits

Information about your health which might identify your child may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator (Dr. Peter Whang)
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at your hospital institution are required to comply with HIPAA and to ensure the confidentiality of your information.

If you choose to participate in this study, the investigators will check your electronic medical record to make sure you qualify. Any access to your electronic medical record will be done consistent with HIPAA regulations.

Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation and Withdrawal

You are free to choose not to participate in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. You do not give up any of your legal rights by signing this form.

Withdrawing From the Study

If you do not become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. This will only occur if you do not attend the assigned weekly sessions.

If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with the Yale School of Medicine and Yale New-Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away permission to use and disclose your health information at any time. You do this by calling or sending written notice to the Principal Investigator, Dr. Peter Whang, Yale Orthopaedics and Rehabilitation, Yale School of Medicine, PO box 208071 New Haven, CT, 06520-8071 United States

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

You do not give up any of your legal rights by signing this form.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: _____

Signature: _____

Relationship: _____

Date: _____

Signature of Principal Investigator

Date

or

Signature of Person Obtaining Consent

Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Peter Whang at (203)-376-9912.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Recruitment Flyer

EXPAREL

FDA approved for surgical wound infiltration (licensed by Pacira Pharmaceuticals)

EXPERIENCE IMPROVEMENT IN POST-OP PAIN

WE ARE CURRENTLY RECRUITING PARTICIPANTS UNDERGOING ELECTIVE POSTERIOR LUMBAR SPINE FUSION FOR A CLINICAL TRIAL EVALUATING THE BENEFIT OF EXPAREL OR LIPOSOMAL BUPIVACAINE IN IMPROVING POSTOPERATIVE OPIOID USE AND PAIN

RECORD OF SUCCESS



Proven safe in animal studies and clinical trials



Research shows sufficient dose dependent blocking of the sensation of pain



Demonstrated efficacy in over 9 other surgical fields

7

Additional studies in spine surgery alone show improvement of pain



Consistent improvement of surgical outcomes across multiple surgical fields



REDUCED COST OF HOSPITALIZATION



EARLIER MOBILIZATION



REDUCED POSTOPERATIVE OPIOID CONSUMPTION



DECREASED POSTOPERATIVE PAIN



SHORTER HOSPITAL LENGTH OF STAY

✉ peter.wang@yale.edu

☎ (203)-376-9912

📍 YALE SCHOOL OF MEDICINE,
PO BOX 208071

If you are interested, please reach out to your orthopedic spine surgery to inquire if you are eligible. For more information, see the link below:

<https://www.pacira.com/products/exparel>

Sample Size Calculation

✓ Power And Precision 4 - [t-test for two independent samples with common variance]

File View Options Tools Scenarios Help

Group	Population Mean	Standard Deviation	N Per Group	Standard Error	95% Lower	95% Upper
Control	93.30	62.70	179			
Intervention	74.64	62.70	179			
Mean Difference	18.66	62.70	358	6.63	5.64	31.68

Alpha= 0.050, Tails= 2

Power

The program displays power

For the given effect size (population means of 93.30 vs. 74.64), SD (62.70), sample sizes (179 and 179), and alpha (0.050, 2-tailed), power is 0.802.

This means that 80% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the two population means are equal.

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Tables and Figures

Table 1: Eligibility Criteria

Inclusion

- Age 18 – 75 years old at the time of screening
- Nonpregnant
- Primary surgical indication for elective open lumbar posterolateral spine fusion is spinal degenerative disease, which includes any of the following:
 - o Spinal stenosis
 - o Spondylolithesis
 - o Radiculopathy/instability disc disorders
 - o Degenerative disc disease
- Medically cleared for elective spine surgery
- Scheduled to undergo primary elective open lumbar posterolateral spine fusion
- Two-level spine fusion
- Active and able to exercise
- ASA physical status classification of 1, 2, or 3
- Cognitively intact and able to provide informed consent, as well as adhere to study assessments

Exclusion

- Significant spinal pathology determined by the investigator that might meaningfully affect postsurgical outcomes, including any of the following:
 - o Suspected cauda equina syndrome
 - o Infection
 - o Primary or metastatic malignancy
 - o Fracture
 - o Systemic inflammatory spondyloarthropathy
- Contraindication to local anesthesia
- History of allergy or hypersensitivity to any of the following study medications utilized:
 - o Bupivacaine
 - o EXPAREL
 - o Tylenol (acetaminophen)
 - o Robaxin
 - o 2 or more nonsteroidal anti-inflammatory drugs
 - o 2 or more gabapentinoids
 - o 2 or more rescue opioids (e.g., oxycodone, morphine, hydromorphone)
 - o 2 or more medications for postoperative nausea, vomiting, or pruritis (e.g., dexamethasone, ondansetron)
- History of severe renal or hepatic impairment
- History of malignancy within 2 years
- History of prior lumbar spine surgery or implanted spinal cord instrumentation (spinal cord stimulator or intrathecal drug pump)
- Planned concurrent surgical procedure or revision spinal surgery
- Anterior surgical approaches

- Lateral surgical approaches
 - Presence of severe comorbid chronic pain condition that requires analgesic treatment and may impact postsurgical outcomes or rehabilitation
 - Any use of long-acting opioids, nonsteroidal anti-inflammatory drugs (except prophylactic 81mg ASA for cardioprotection) within three days of screening
 - Any use of short-acting opioids within 24 hours of screening
 - High dose presurgical opioid use (mean daily intake >100mg mEq PO within past 30 days)
 - History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol as defined in the DSM-5
 - Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration
 - Body Mass Index < 17 kg/m² or > 44 kg/m² at screening
 - Subjects receiving Worker's Compensation for disability or involved with litigation related to the spine
 - Prior participation in an EXPAREL study
 - Administration or planned administration of any other investigational drug within 30 days or 5 elimination half-lives prior to study drug administration during the subject's participation in this study
- ** In addition, the subject may be excluded from study prior to study drug infiltration if any of the following criteria during the surgical procedure are met:*
- a) Inability to place planned surgical instrumentation
 - b) Poor fixation at the time of surgical instrumentation
- ** In addition, the subject may be terminated early if any of the following criteria after the surgical procedure are met:*
- a) Incision size > 20cm
 - b) Autograft taken from harvest site other than surgical site
 - c) Intraoperative complications likely to meaningfully affect postsurgical outcome, including any of the following:
 - I. Clinically significant and prolonged (i.e., >24 hours) neurologic deficit
 - II. Dural tear or suspected dural tear requiring bed rest
 - III. Extensive bleeding (i.e., >1000ml blood loss)
 - IV. Symptomatic epidural hematoma
-
-

Table 2: Other Descriptive Measures

Patient Characteristics

Age, gender, race, BMI, ASA classification, baseline VAS score, comorbidities, smoker status, opioid naivety

Surgery Characteristics

Surgery type, duration of surgery, total incision length, blood loss

Table 3: Subject Baseline Characteristics and Analysis Method

		Intervention	Control	P-value
Patient Characteristics	Age	N (%)	N (%)	Chisquare test
	Gender	N (%)	N (%)	Chisquare test
	Race	N (%)	N (%)	Chisquare test
	BMI	Mean \pm SD	Mean \pm SD	Independent T test
	ASA classification	N (%) N (%) N (%)	N (%) N (%) N (%)	Chisquare test
	Baseline VAS score	N (%)	N (%)	Chisquare test
	Comorbidities	N (%)	N (%)	Chisquare test
	Smoker status	N (%)	N (%)	Chisquare test
	Opioid naivety	N (%)	N (%)	Chisquare test
Surgery Characteristics	Surgery type	N (%)	N (%)	Chisquare test
	Duration of surgery	Mean \pm SD	Mean \pm SD	Independent T test
	Total incision length	Mean \pm SD	Mean \pm SD	Independent T test
	Blood loss	Mean \pm SD	Mean \pm SD	Independent T test

Table 4: Primary Outcomes and Analysis Method

	Intervention	Control	P-value
Total Postoperative Opioid use 0 – 72 hours	Mean \pm SD	Mean \pm SD	Independent T test

Table 5: Secondary Outcomes and Analysis Method

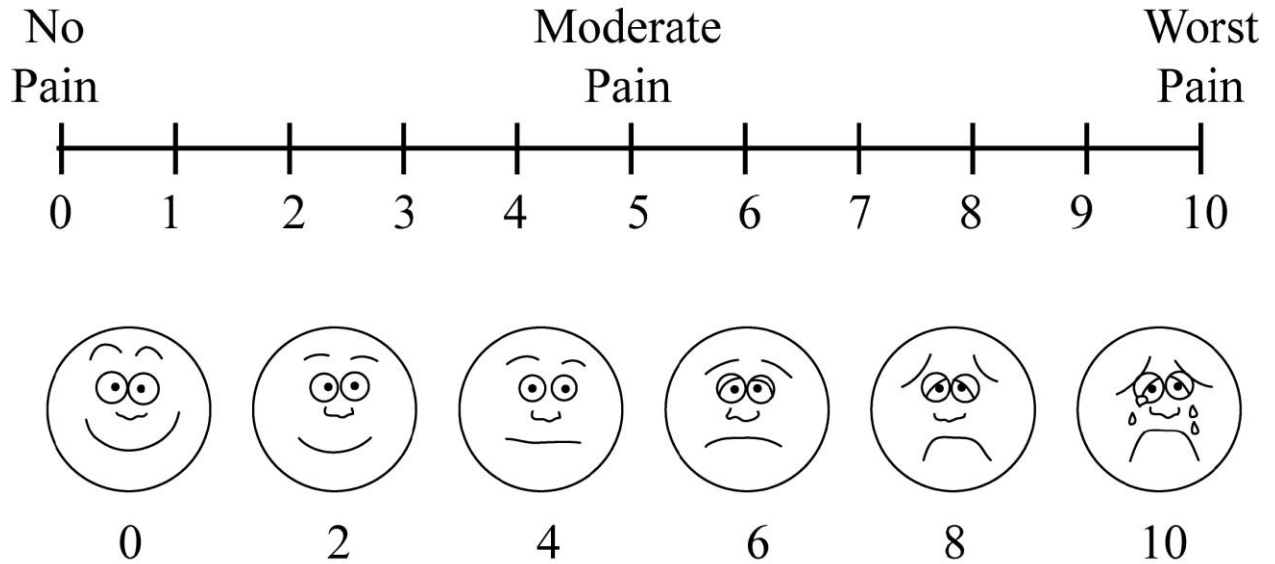
	Intervention	Control	P-value
Total Postoperative opioid use at 14 days	Mean \pm SD	Mean \pm SD	Independent T test
Number of opioid related adverse events (OR-SDS)	Mean \pm SD	Mean \pm SD	Independent T test
Area under the curve (AUC) of Pain Intensity scores (via VAS)	Mean \pm SD	Mean \pm SD	Independent T test
Time to first opioid rescue through 72 hours or discharge	Mean \pm SD	Mean \pm SD	Kaplan-Meier Analysis

Table 6: Health Outcomes and Analysis Method

	Intervention	Control	P-value
Total length of stay	Mean \pm SD	Mean \pm SD	Independent T test
30 days all cause readmissions	Mean \pm SD	Mean \pm SD	Independent T test
30 days readmissions related to pain	Mean \pm SD	Mean \pm SD	Independent T test
14 days office visits or calls to doctor related to pain	Mean \pm SD	Mean \pm SD	Independent T test
Total time spent in PACU or SDU	Mean \pm SD	Mean \pm SD	Independent T test
Discharge Readiness	N (%)	N (%)	Chisquare test
Discharge Disposition	N (%)	N (%)	Chisquare test

Visual Analog Scale Pain Score sheet

Daily Pain Assessment



IM: Palliative Care. Visual Analog Scale. Yale University.
<https://assessment-module.yale.edu/im-palliative/visual-analogue-scale> Updated 2020. Accessed June 18, 2020.

Date of Score: _____

Time of Score: _____

Scorer: _____

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