INTRAOPERATIVE LOCAL INFILTRATION OF EXPAREL VERSUS INTERSCALENE BRACHIAL PLEXUS BLOCK FOR POSTOPERATIVE PAIN CONTROL IN TOTAL SHOULDER ARTHROPLASTY: A SYSTEMATIC REVIEW

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Candidates' Names: Matthew Merrill and Jacob Palmer

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Abstract

Patients undergoing Total Shoulder Arthroplasty (TSA) report significant postoperative pain, and various methods have been used to reduce this pain. Pacira Pharmaceuticals Inc. has recently introduced Liposomal Bupivacaine (Exparel) with reports of up to 72 hours of postoperative pain relief when used as a regional blockade. The researchers in this study performed a systematic review of the literature to determine if postoperative pain scores, total opioid consumption, and length of hospital stay were decreased with the use of Exparel as an intraoperative local infiltration (ILI) versus interscalene brachial plexus block (ISBPB) with Bupivacaine HCl for patients undergoing total shoulder arthroplasty (TSA). Method: Articles were obtained through online database search resulting in six studies comparing the two methods. Results: Pain scores, opioid consumption, and length of hospital stay did not differ between the two study groups. Conclusion: With the added cost of using Exparel and a lack of improved outcomes for patients it is not found to be a beneficial method of providing regional blockade for TSA.
Chapter 1

Introduction

Anesthesia for orthopedic surgery is in high demand with the aging population. Orthopedic procedures such as total shoulder arthroplasties (TSA) can be especially painful for patients during the postoperative period. Interscalene brachial plexus blocks (ISBPB) have been shown to be an effective anesthetic technique for shoulder surgery. These blocks are commonly used to assist anesthetic management and postoperative pain for TSA procedures. ISBPB is used to provide anesthesia and inhibit neuronal activity of nerves arising from the 5th through the 8th cervical vertebrae and 1st thoracic vertebrae. The major brachial plexus nerves anesthetized are the axillary, musculocutaneous, radial, and median. When appropriately anesthetized, full motor and sensory blockade ensues from the posterior portions of the shoulder and clavicle down through the fingers.

Bupivacaine HCl is a common local anesthetic used for interscalene blocks primarily due to its duration of action. However, liposome bupivacaine (Exparel), which is a fairly new local anesthetic on the market, has proven to be superior in duration of action to all other local anesthetics. Exparel works by slow continuous release of local anesthetic from housing lipid molecules. This causes prolonged effects through less systemic uptake of the local anesthetic, thereby leaving more of the active drug at the desired location. Although Exparel has proven to be superior, some facilities and anesthesia providers still chose to use Bupivacaine HCl for interscalene blockade.

Other than assisting with anesthetic management, peripheral nerve blocks are performed to provide less postoperative pain and more comfort to the patient. It is common practice for
anesthesia providers to advise patients receiving interscalene blockade with Bupivacaine HCl for TSA to begin consuming opioids as early as the evening on the same day as surgery. This leads to more opioid consumption and accompanying negative side effects such as nausea, constipation, and reduced feelings of self-control. To extend pain relief for the patient and decrease opioid consumption, Exparel can be injected into the tissue surrounding the operative site versus an interscalene block with bupivacaine HCl in patients undergoing shoulder arthroplasty.

**Problem Statement, Background, and Significance**

Upper extremity orthopedic surgery is associated with moderate to severe postoperative pain.\(^2\) Attempts to optimize analgesia and minimize opioid related side effects are the cornerstones of postoperative patient management in those undergoing TSA.\(^2\) One of the primary attempts at optimizing analgesia and minimizing opioid related side effects is the use of regional anesthesia techniques. With the growing opioid epidemic, national focus has shifted to the use and misuse of opioids in all areas of medicine.\(^3\) Regional anesthesia offers sufficient analgesia during the hospital stay for shoulder arthroplasty procedures while adhering to high patient comfort and satisfaction.\(^1\) The ideal regional anesthetic technique provides dense intraoperative anesthesia, postoperative analgesia, and minimization of motor block.\(^2\) Although regional anesthesia is highly effective, current long-acting local anesthetics are associated with a relatively short duration of analgesia.\(^2\)

Patients who receive ISBPB spend less time in the post anesthesia care unit (PACU), have high levels of satisfaction with their anesthesia, need less postoperative analgesics, and
have shorter hospital stays.\(^1\) ISBPB is an effective anesthetic technique for TSA that is typically associated with minimal opioid utilization both intraoperatively and for the first hours after surgery.\(^3\) Rebound pain is an acute pain phenomenon that is encountered during the first few hours after the effects of an ISBPB dissipate.\(^3\) When rebound pain occurs, it commonly results in a sharp spike in narcotic utilization and increase in pain scores from 8 to 24 hours after TSA.\(^3\) The efficacy of Exparel in various surgical populations has indicated a potential for activity for up to 72 hours after surgery.\(^3\)

ISBPB is known to provide excellent pain relief for the first 8 hours after surgery. Unfortunately, the benefits of the ISBPB subside beyond 8 hours, and rebound pain can dramatically increase the patient’s postoperative pain experience and narcotic consumption. Infiltration of the soft tissues with Exparel alone is known to yield a more consistent pain experience during the first 24 hours after surgery, but worse pain scores between 0 and 8 hours compared with those for patients treated with ISBPB. For these reasons, a combined approach that includes both ISBPB and injected Exparel could optimize both early and delayed pain experience following TSA.\(^3\)

Due to limited approval by the US Food and Drug Administration, Exparel is still a new drug that has not been used by many anesthesia providers.\(^3\) This study could offer insight as to whether Exparel is an effective adjunct in regional anesthesia. This study is important for the field of anesthesia because it could improve patient outcomes and satisfaction and decrease postoperative opioid consumption. The findings of this study could offer evidence-based practice data for anesthesia providers to make informed decisions on treatment choices. Anesthesia
providers are the primary deliverers of pain relief for the patient throughout the perioperative period; therefore, the findings of this study could positively modify current practice techniques. Anesthesia providers could be able to offer longer pain relief with the use of Exparel which would increase patient comfort and satisfaction and decrease opioid consumption.

**Purpose**

The purpose of this study was to compare two methods of regional anesthesia used to provide postoperative pain relief and decrease opioid consumption in patients undergoing total shoulder arthroplasty. These two methods were ISBPB with Bupivacaine HCl or ILI using Exparel and Bupivacaine HCl as the local anesthetic component. This study was carried out with a systematic review comparing these two methods. The data collected allowed for a clearer understanding of which anesthetic method is superior in providing postoperative pain relief and decreased opioid consumption during this time. If the use of Exparel proves to be a better method of anesthesia, the stance could be made that it should be used for patients undergoing TSA. This argument is based on documented research showing the extended duration of action of Exparel.

**Theoretical Framework**

The theoretical framework for this study was based on the Theory of Preemptive Analgesia. Pain modulation is a complex idea first described by Dr. George Washington Crile in 1914. Crile was an Ohio born surgeon who spent his life's work on documenting the effects of pain on the human body. His first publication described a theory on how to prevent pain related to surgery, improve safety for the patient, and decrease post-surgical complications. He termed
this process Anoci-association, or absence of damaging associations. Crile had success with this technique while performing thyroid surgery by sedating the patient with morphine and ether prior to moving to the operating room. Later, he added infiltration of cocaine to the surgical site prior to incision to blunt the nociception of surgical trauma. He concluded that by blocking the nociception of pain before pain ever occurs reduced the degree of change in the central nervous system following surgery. His observations are a large determinant of using regional anesthesia in conjunction with general anesthesia to provide maximum relief to patients undergoing surgery today.

To further understand the framework of preemptive analgesia it is important to discuss some terms related to pain modulation. When a noxious stimulus occurs, in this case the surgical incision, a signal is sent along afferent peripheral pain receptors towards the dorsal horn of the spinal cord. This signal is received by a first order neuron in the dorsal root ganglia. The signal then travels by way of the Lisser tract, moving one to three levels on the ipsilateral side, and synapses with a second order neuron in the substantia gelatinosa in lamina II and III. The second order neuron will then carry the pain stimulus contralateral before ascending the spinothalamic tract. A synapse with the third order neuron occurs in the thalamus and reticular activating system. The pain signal is then sent and interpreted by the cerebral cortex. Central sensitization can occur when a painful stimulus or inflammatory injury leads to central nervous system changes resulting in hypersensitivity. After central sensitization is present a state of hyperexcitability may occur, resulting in allodynia and hyperalgesia. Alldynia and hyperalgesia can both result in chronic changes that are altering for patients.
As Crile first discovered when employing the Theory of Preemptive Analgesia, if interventions are performed to establish a sensory blockade prior to the noxious stimuli Anesthetists are able to prevent central sensitization from occurring. In the case of this study, local anesthetic will be deposited around a plexus of nerves that provides motor and relays sensory information from the arm and shoulder. As the local anesthetic acts upon the nerves any pain modulation that occurs distal to the site of blockade will be temporarily interrupted. With the inability of peripheral receptors to modulate a pain signal to the first order neuron the body will be unaware it is experiencing pain.

**Research Questions**

Will intraoperative local infiltration (ILI) of liposome bupivacaine (Exparel) reduce post-operative opioid consumption for patients undergoing shoulder arthroplasty when compared to an interscalene brachial plexus block alone?

Will intraoperative local infiltration (ILI) of liposome bupivacaine (Exparel) reduce post-operative pain scores for patients undergoing shoulder arthroplasty when compared to an interscalene brachial plexus block alone?

Will intraoperative local infiltration (ILI) of liposome bupivacaine (Exparel) reduce hospital length of stay for patients undergoing shoulder arthroplasty when compared to an interscalene brachial plexus block alone?

**Definitions**
**Interscalene Brachial Plexus block (ISBPB):** Technique which allows for blockade of the brachial plexus, providing surgical anesthesia and post-operative pain control of the shoulder and upper arm. This approach will be accomplished with ultrasound guidance by locating the nerve roots of C5, C6, C7, and C8 and T1 between the middle scalene and anterior scalene muscles. Commonly, nerve stimulation is utilized along with ultrasound guidance. In this scenario, as the needle enters the prevertebral fascia, a muscle twitch will be elicited in the shoulder and upper arm, further confirming appropriate placement. This area is then infiltrated with 15-40 ml of the desired local anesthetic to provide the desired effect.

**Liposome Bupivacaine (Exparel):** A local anesthetic medication belonging to the group known as amide local anesthetics. This newly released form of Bupivacaine is liposomally encapsulated in a substance known as DepoFoam. This allows for the slow release of Bupivacaine over a 96-hour period. This slow release mechanism also acts as a safety marker, decreasing plasma levels of Bupivacaine. Exparel comes in a single concentration of 13.3mg/ml. It is commonly mixed with standard bupivacaine in a 2:1 ratio or diluted into large volumes with normal saline or lactated ringer, but it cannot be mixed with any other medications.

**Bupivacaine HCl:** A local anesthetic medication belonging to the group known as amide local anesthetics. Bupivacaine HCl is in an aqueous state and after injection can move into surrounding tissues. It is manufactured in different concentrations, but for this study researchers will only be examining 0.25% and 0.5% concentrations. Duration of action is 4 – 16 hours.
Intraoperative local infiltration (ILI): injection performed by the surgeon prior to closing of the surgical wound. Medication is administered through injection, providing local blockade of the tissue at the surgical site.

Postoperative opioid consumption: Amount of opioid analgesic medication taken after surgery is completed from the time of admission to post anesthesia care unit to hospital discharge. All opioid analgesic medications administered will be converted into Morphine equivalent dosage.

Postoperative pain score: Self-reported pain scores will be supplied by the patient at intermittent, predetermined intervals starting upon admission to the post anesthesia care unit up to the time of hospital discharge.

Length of hospital stay: Time of admission to the hospital for surgery to the time of discharge from the hospital.

Scope and Limitations

The researchers in this study conducted a systematic review that maintained a narrow scope. Studies were chosen using the online search databases of EbscoHost, PubMed, Cinahl, and Medline with the key search words of; total shoulder arthroplasty, slow release bupivacaine, liposome bupivacaine, Exparel, interscalene, and brachial plexus block. Selection of articles were then determined based upon the pertinent information they provide to the systematic review. Inclusion criteria was randomized controlled trials and retrospective cohort reviews with adult patients undergoing total shoulder arthroplasty, information about postoperative pain scores, postoperative opioid consumption, and hospital length of stay. Exclusion criteria was any
study including surgeries other than total shoulder arthroplasty, revision total shoulder arthroplasty, and case studies examining the use of Exparel.

Limitations were present for this systematic review. Data collected was from studies already completed, therefore, manipulation of interventions received by patients was not available. Sample sizes, the degree of randomization, dosages of nerve block medications, and techniques for administration of ISBPB and ILI vary between studies. Pain score evaluations between studies may be altered due to the subjective nature and varying pain tolerances between individuals. One additional limiting factor is that some studies included in the systematic review used continuous interscalene catheters when others elected to use only single-injection ISBPB.

**Summary**

This study determined whether injectable Exparel provided adequate analgesic effects and minimized opioid consumption in patients undergoing TSA when compared to outcomes from patients receiving an ISBPB. Patient comfort and satisfaction is at the center of the healthcare system, therefore, Exparel should be used if it adds density and time to the regional blockade. Data for the study was collected using a systematic review of studies conducted outlining this information. Researchers investigated whether the ILI of Exparel would decrease postoperative opioid consumption, improve pain score ratings, and decrease length of stay following shoulder arthroplasty. Depending on the results, anesthesia colleagues and peers would be able to make informed treatment decisions based on current data.
Introduction

Patients who are undergoing surgery on the shoulder will undoubtedly have discomfort afterwards. Generally, with TSA efforts are made preoperatively to provide these patients with some form of preemptive analgesia. The most common measure taken is an ISBPB prior to the procedure. Although the ISBPB has been routinely used for some time to help prevent and control post-operative pain, this method does not come without possible negative outcomes. Neurologic damage can occur leading to long term complications, and postoperative respiratory issues can arise due to the diaphragmatic involvement from phrenic nerve blockade. A new modification of the local anesthetic bupivacaine has introduced the possibility of achieving the same analgesic relief without these risks associated with performing the ISBPB. Exparel can be administered by local infiltration into the surgical site by the surgeon and the literature suggests equal benefits of analgesic relief. This systematic review of multiple randomized controlled trials will evaluate the differences in post-operative pain scores, opioid consumption, and length of hospital stay between groups that received only an ISBPB and those that received ILI of Exparel.

Key Literature Topics

Primary analgesia for a patient undergoing a TSA involves a sensory and motor blockade of the upper extremity. This can be accomplished effectively by performing an ISBPB prior to surgery. Some surgeons may also prefer the anesthetist to place a catheter that can provide a small dose of continuous local anesthetic medication postoperatively. Another technique utilized by some surgeons is to infiltrate the surgical site with a “cocktail” of medications prior to closing
of the surgical wound after completion of the surgery. This cocktail will vary depending on the surgeon's preference, but can include opioids, anti-inflammatory medication, local anesthetics, and vasoconstrictors. Exparel has become a promising option in place of this cocktail injection. When using Exparel as an ILI for postoperative pain relief the surgeon uses a standardized protocol making small volume injections of 1-2 ml around the surgical site every 1-1.5 cm. Total volume of the injection will depend on the size of the wound, but total dosage must not exceed 266 mg of Exparel. To allow for the appropriate volume in larger surgical site coverage the 20 ml vial of Exparel, which contains 266mg, can be further diluted with normal saline or lactated ringer solution up to a total volume of 300 ml. Additionally, since Exparel is a slow release formula Bupivacaine HCl can be added to hasten the onset as long as the total milligram dosage of Bupivacaine HCl does not exceed a 2:1 ratio of the Exparel dosage. Multiple injections are needed to provide adequate coverage because the Exparel solution does not disperse into surrounding tissues like the other aqueous solutions such as Bupivacaine HCl or cocktail mixtures. When using the Exparel technique some studies have suggested analgesia up to 72 hours postoperatively.

Although the ISBPB has been shown to provide significant intraoperative and immediate postoperative analgesia, the technique still has drawbacks. To perform an ISBPB the anesthesia provider must be competent in the anatomy and use of either ultrasound guidance or nerve stimulation technique. Due to these variables block failure is a concern. Data has also shown the phenomenon of rebound pain which can occur around the 24th postoperative hour.

Studies and Findings
Namdari et al conducted a non-blinded randomized controlled trial of 156 patients undergoing total shoulder arthroplasty to investigate the consumption of intraoperative and postoperative opioids, postoperative pain scores, and hospital length of stay between two groups of participants. The two groups of 78 participants were randomized using a computerized number generator. Group 1 participants (blockade group) received an ISBPB preoperatively using 30ml of 0.5% ropivacaine. Blocks were performed by 1 of 6 anesthesiologist who were proficient in the use of ultrasound guidance regional anesthesia. Group 2 (Exparel group) received an ILI of a suspension with 266 mg of Exparel diluted to a total volume of 40 ml. 1 of 4 fellowship trained orthopedic surgeons performed the TSA and administered the Exparel. A moving needle technique was used with multiple 0.5 ml injections within and around the surgical site upon completion of the surgery. For both study groups, the intraoperative opioid administration was directed by the anesthesiologist based upon indicators for pain, such as increased blood pressure or heart rate. All patients from both groups were given a patient-controlled analgesia pump in the recovery room consisting of hydromorphone. If the patient had a known allergy to hydromorphone, they received either fentanyl or morphine. The authors of the study then began to analyze the data and used morphine-equivalent dosing to determine the total amount of opioids consumed by the patient over the first 24 hours postoperatively, and visual analog scores (VAS) for pain were assessed at 0, 8, 16, and 24 hours postoperatively.

A two-tailed t test was utilized to adjust for two primary outcomes being tested independently. To account for continuous variables the Mann-Whitney test was used, and the Fisher exact test was used for non-continuous variables. A linear regression model determined
correlations between demographic variables, morphine equivalent units consumed, and VAS pain scores. All analyses were performed using R foundation. Significance was defined as a p value of 0.025.\textsuperscript{3} Total postoperative opioid consumption in the first 24 hours showed no difference between the two groups (p = 0.849).\textsuperscript{3} Intraoperative opioids were significantly lower in the group that received an ISBPB with total requirement half of what the ILI group received (p < 0.001).\textsuperscript{3} Additionally, the overall opioid consumption was significantly lower in the group that received an ISBPB (p < 0.001).\textsuperscript{3} The VAS pain scores were significantly lower at hours 0 and 8 (p < 0.001) in the blockade group.\textsuperscript{3} No difference was seen in VAS pain scores at 16 hours (p = 0.348) but they were significantly higher in the blockade group at 24 hours (p = 0.021).\textsuperscript{3} The authors attributed this trend to the effects of rebound pain in the blockade group. No significance was determined in the length of hospital stay between the two groups (p = 0.293).\textsuperscript{3} The authors concluded that ILI with Exparel is a viable option for postoperative pain relief in place of an ISBPB. However, intraoperative requirements for opioids are likely to be increased. Additionally, postoperative effects of adequate pain relief with ILI are unpredictable up to 8 hours but no reports of rebound pain are seen.

Okoroha et al\textsuperscript{9} from the department of Orthopaedic Surgery at Henry Ford Hospital in Detroit, Michigan performed a prospective randomized trial of 57 patients undergoing total shoulder arthroplasty. The authors of this study hypothesized that patients would have no significant differences in pain scores whether the primary postoperative analgesic method was the use of ILI with Exparel versus ISBPB with 0.5% ropivacaine. Inclusion criteria for study participants included adults over the age of 18 undergoing either total shoulder or reverse total shoulder arthroplasty. Patients were excluded as candidates for known allergies to decadron,
ropivacaine, or bupivacaine; substance abuse history, and pregnancy. A computerized algorithm was used to randomize patients into two groups with a final determination of 31 patients who would receive ISBPB and 26 patients that would receive an ILI of Exparel. The surgery was then performed by 1 of 3 fellowship trained shoulder surgeons. These surgeons administered the ILI of Exparel using the standardized protocol upon completion of the surgery and prior to closing the surgical wound. Each patient in the ILI group received a total volume of 40 ml mixture containing 266 mg of Exparel and 20 ml of normal saline. For the ISBPB group a certified anesthesiologist with utilized the ultrasound guidance technique to inject a single dose of 40 ml 0.5% ropivacaine into the brachial plexus nerve sheath. Once the patient arrived in the PACU pain levels and opioid consumption was monitored every hour for four hours, then every four hours thereafter using the VAS. Upon admission to the orthopedic floor all participants were started on postoperative pain regimens of 650 mg tylenol every 8 hours, oxycodone 5 mg every 4 hours as needed for pain less than 5-out-of-10, oxycodone 10 mg every 4 hours as needed for pain greater than 5-out-of-10, and morphine 2 mg IV every 4 hours as needed for severe breakthrough pain. These measurements were documented for four days postoperatively and all opioids consumed by the patient were converted into morphine equivalent units. Hospital length of stay was also recorded for all participants. If patients were discharged home prior to the third day postoperatively a binder was sent home with them to document pain scores and opioid consumption for the remaining days.

For statistical analysis R 3.2.1 software was used to compare demographic variables, VAS scores, and IV morphine equivalent units with a two-tailed t test using mean and standard deviation when appropriate. Statistically significant findings were defined as a P value < 0.05.
Demographic data included number of patients, age, male to female ratio, and BMI. No
significance was noted in this area with a p = 0.89. VAS pain scores were significantly higher in
the Exparel ILI group for the first 8 hours postoperatively (p=0.001). However, at 21 hours
postoperatively the VAS was significantly higher for the ISBPB group (p = 0.18). After the
24-hour mark up to the end of the study, no significant difference was noted in VAS pain scores
between the two groups (p value on POD 1 = 0.21, POD 2 =0.34, and POD 3 = 0.85). Total
opioid consumption was decreased in the Exparel ILI group in the first 24 hours (p = 0.02) with
the greatest difference noted at hours 13-16 postoperatively. POD 1 showed no significant
difference in opioid consumption (p = 0.95), but an increasing trend was seen in the Exparel ILI
group on POD 2 at hours 49-56 postoperative (p = 0.02). No significance was seen in the
difference of hospital stay between the two groups (p = 0.97). The authors of this study
concluded that increased VAS pain scores are expected during the first 8 hours postoperatively
due to the slow release of Exparel when compared to participants receiving an ISBPB. However,
after this initial period ILI with Exparel showed a more consistent analgesia and decreased
opioid consumption of the day of surgery. After the day of surgery, the authors discovered no
significant difference in VAS pain scores, opioid consumption, or hospital length of stay
between the two groups.

Angerame et al\textsuperscript{13} from the Department of Orthopedic Surgery at the Carolinas Medical
Center in Charlotte, North Carolina conducted a retrospective chart review of 69 patients who
underwent total shoulder arthroplasty between January 2013 and April 2015. The authors
examined differences in Numeric Pain Rating Scale (NPRS) score, length-of-stay-, and morphine
equivalent opioid consumption of patients who either received ILI with Exparel or one-time
preoperative ISBPB. Participants were included in the study if they were over 18 years old and undergoing unilateral primary total shoulder arthroplasty. Patients were excluded from the study if a prolonged hospital stay was required for reasons related to comorbid disease unrelated to the TSA. At the time of surgery, patients chose to receive either the ILI with Exparel or ISPBP after risks and benefits of each were explained by the surgeon performing the TSA. This method produced two cohorts; 44 patients chose to receive an ISBPB and 25 patients chose ILI with Exparel. To standardize results, the authors chose to review charts from only one fellowship trained shoulder and elbow surgeon. The Exparel ILI group injections consisted of 20 ml of Exparel (266 mg) and 20 ml of 0.25% bupivacaine and were performed by the surgeon upon the completion of surgery prior to closure of the wound using the standardized protocol. 

The authors collected data from the electronic medical record to evaluate NPRS score which was average across 12-hour increments to adjust for inconsistent documentation. Postoperative opioids were administered on an as-needed basis only with no schedule regimen or patient controlled analgesia pump. Opioid use was recorded and then converted into morphine equivalent units. The Wilcoxon tests were utilized to evaluate differences in length of stay, total morphine equivalents. Chi-square test was used to evaluate demographic differences. Demographic data including age, sex, ASA physical status, and preoperative opioid use showed no significant differences (p = 0.81). The total postoperative morphine equivalents for both groups were around 130 and showed no significant difference (p = 0.71). Pain scores for the Exparel group in the first 12 hours after surgery were lower than the ISBPB group, but clinical significance was not found (p = 0.25). Between 13 and 34 hours after surgery the Exparel group had slightly higher pain scores (p = 1.00). For the remainder of time monitored, pain scores has
no discernable difference between the two groups (p = 1.00) Average length of hospital stay for ISBPB group was 48 hours while it was 49 hours for the Exparel group (p = 0.33). The authors of this study concluded that ILI with Exparel is a viable option in place of ISBPB to control postoperative pain, reduce the consumption of opioids, and avoid possible complications and cost associated with ISBPB.

Sabesan et al conducted a prospective randomized controlled clinical trial comparing consecutive patients undergoing shoulder arthroplasty treated with interscalene nerve blockade vs. liposomal bupivacaine with a single bolus interscalene block. The goal of the trial was to assess the impact of liposomal bupivacaine compared with interscalene nerve block (ISB) in terms of postoperative pain control, outpatient pain scores, and patient-reported and functional outcomes after shoulder arthroplasty surgery. This study included 70 consecutive shoulder arthroplasty patients from August 2015 through June 2016 during the period of one year. All patients undergoing shoulder arthroplasty were enrolled in the study if they met the inclusion criteria of being 18 years or older and met the standard of care of ISB per anesthesia guidelines issued by the American Society of Anesthesiologists. Exclusion criteria included contraindications to regional anesthesia, allergy to any component of multimodal analgesia, history of opioid use of > 50 morphine milligram equivalents (MME) daily, significant peripheral neuropathy or neurologic disorder affecting the upper extremity, cognitive or psychiatric condition that might affect the patient’s assessment or inability to provide informed consent. Patients were prospectively randomized into 1 of 2 pain management groups using a computer randomization program, Google Coin Flip.
There were 36 patients in the ISB group and 34 patients in the liposomal bupivacaine group. There was no significant difference noted in postoperative pain control of opioid consumption within the first 24 hours. One limitation to the study is the use of the Numeric Rating Scale (NRS) pain scale has been associated with higher patient-reported pain scores with little ability to detect subtle changes. Also, surgeons were not blinded to intervention because the surgeon had to perform the intra-articular injection. This trial helps shed light onto the use of liposomal bupivacaine and the potential it possesses. It also supports the theory that liposomal bupivacaine can be extremely effective at managing postoperative pain.\textsuperscript{14}

Abildgaard er al\textsuperscript{15} conducted a prospective randomized controlled trial comparing the effectiveness of liposomal bupivacaine (LB) vs. interscalene nerve block (INB) with bupivacaine. The goal of this study was to observe whether or not the use of LB would improve immediate postoperative pain control when compared to bupivacaine. It was stated that LB is an extended-release delivery of a phospholipid bilayer encapsulating bupivacaine that can result in drug delivery up to 72 hours.\textsuperscript{15} Due to the extended release of the drug, a bridge of 30 mL of 0.5% bupivacaine was added to the blocks of the patients receiving LB. The study consisted of 83 consecutive shoulder arthroplasty patients with 36 patients receiving LB and 47 patients receiving INB with bupivacaine. Postoperative visual analog scale (VAS) pain levels, opiate consumption measured with oral morphine equivalents, length of hospital stay, and postoperative complications were recorded. Patients who were older than 18 years and candidates for a total shoulder arthroplasty with either an anatomic or reverse prosthesis were eligible for enrollment. Study exclusions criteria included pregnancy and patients with hepatic disease. A random number generator was used to establish a randomization list before the start of enrollment.
Ninety-six patients were recruited for enrollment in this trial with 13 dropping out. 12 from the LB group and 1 from the INB group.\textsuperscript{15}

The highest VAS score in the PACU was recorded as a reflection of the worst immediate postoperative pain experienced. Remaining VAS scores once patients left the PACU were averaged for each postoperative day. Narcotic pain medications were converted to oral morphine equivalents (OMEs) on the basis of published tables enabling different narcotic medications to be converted to a standardized narcotic quantity. The study concluded that pain scores were statistically higher in the LB cohort immediately postoperatively in the PACU. Narcotic use was also higher in the LB group. However, there was no statistical difference in the length of hospital stay among both groups.\textsuperscript{15}

Hannan et al\textsuperscript{16} conducted a retrospective cohort analysis with 58 patients who underwent shoulder arthroplasty. The purpose of the study was to compare intraoperative local liposomal bupivacaine injection with preoperative single-shot interscalene nerve block (ISNB) in terms of pain control, opioid use, and length of hospital stay (LOS) after shoulder arthroplasty. The study included 37 patients who received liposomal bupivacaine and 21 patients who received ISNB. Patients who underwent TSA, reverse TSA, or hemiarthroplasty of the shoulder were included. Patients who underwent revision TSA were excluded from the study. Limitations of the study included the retrospective design, relatively small numbers of patients in each group, variations in the types of procedures in each group, and lack of long-term outcome measures.\textsuperscript{16}

Results of the study 8-14 hours postoperatively showed no significant difference in pain scores between the two groups. There was also no difference in the amount of opioid
consumption during this time. However, the liposomal bupivacaine patients reported less pain at 18-24 hours and 27-36 hours and has less opioid consumption. Final results showed that liposomal bupivacaine was associated with less pain, less opioid consumption, and shorter hospital stays after shoulder arthroplasty compared with ISNB.\textsuperscript{16}

**Gaps and Omissions**

Many studies exist examining the efficacy of Exparel, however, the majority of these studies consist of small sample sizes. Narrowing down the type of shoulder arthroplasty also seemed to be an issue during the literature review. This led to varying information regarding the effectiveness of Exparel when compared to other local anesthetics. Through this review process it has become apparent that larger sample sizes and narrower surgical criteria are needed to more thoroughly conclude the effectiveness of liposomal bupivacaine.

**Summary**

In conclusion, the annual number of TSA is rising with the growing elderly population, and pain control after these procedures is challenging.\textsuperscript{16} Exparel has been associated with less pain and opioid consumption in patients following TSA\textsuperscript{16} However, there is still debate regarding the medications effectiveness due to small sample sizes of patients being studied and the surgical approach the patients receive. Exparel is a fairly new medication on the market, and its effectiveness continues to remain controversial. It is well understood that regional anesthesia for TSA is intended to provide adequate pain relief during the early postoperative period in an effort to expedite patient recovery and increase satisfaction. Theoretically, Exparel possesses the capability of providing analgesia throughout the early postoperative period, and as long as 72
hours. The current body of knowledge is lacking in larger patient-size comparative studies. The majority of the sample sizes are small, and the surgical technique used is broad. However, current findings suggest that Exparel is a promising drug with abundant benefits in providing adequate analgesia in comparison to other local anesthetics.
Chapter 3

Project Design

The researchers conducted a quantitative correlational systematic review of prospective randomized control trials and retrospective cohort review of patients undergoing TSA. Comparisons were made while looking at postoperative pain scores, total opioid consumption, and length of hospital stay between groups receiving either surgical site ILI of Exparel or a preoperative ISBPB. In this study, the independent variables were the use of ILI with Exparel versus ISBPB. Dependent variables will be measured as postoperative pain scores, total opioid consumption, and length of hospital stay.

Instruments

Information was gathered by thoroughly searching for research articles from the EBSCOhost database of the Newman library. The databases searched included CINAHL Complete, PubMed, MEDLINE, and UpToDate. Articles that met the study criteria were then kept for inclusion in the systematic review. Articles kept for inclusion were those of which specifically compared the use of Exparel to other local anesthetics in total shoulder arthroplasty. All articles were from respected journals and valid. Variables that are important to the study will be grouped into sections to include type of local anesthetic, surgical approach, postoperative pain scores, opioid consumption, and length of hospital stay.

Sample & Sampling Procedure

In this study the researchers utilized a convenience sample obtained from multiple online search databases as stated above. Included studies were those where patients underwent TSA
where ILI of Exparel versus preoperative ISBPB was utilized for the primary method of postoperative pain reduction. Inclusion criteria for the sample was not exclusively defined by the ASA-physical status, patient age, patient gender, specific dosages of medications, or cocktail of medications utilized in the ILI or ISBPB. The researchers understand this is a limitation to the study, however, this was an uncontrolled variable as the data that was obtained had reached completion of study. Previous studies were excluded if they examined surgeries other than TSA or reverse TSA, or utilized methods for postoperative pain control other than ILI of Exparel or ISBPB.

The sample for this study was obtained by using the key search words of: total shoulder arthroplasty, slow release bupivacaine, liposome bupivacaine, Exparel, interscalene, and brachial plexus block. Inclusion criteria for this systematic review included only studies for TSA or reverse TSA. Any studies looking at other types of shoulder surgery or studies researching methods for postoperative pain reduction other than ISBPB or ILI of Exparel were excluded. Of the 3,669 articles obtained using these key search words the researchers excluded all but six to further examine for this systematic review. Four prospective randomized control trials and two retrospective cohort reviews specifically compare outcomes between 493 patients who received either ILI with Exparel or ISBPB. The researchers believe this sample size provided adequate information to form a comparison between the two modalities for postoperative pain control.

**Management and Analysis Plan**

Information for the study was gathered from research articles found through the Newman library database. The study possessed no risk to human subjects because all information was
collected from published research articles. The study required no subject participation or consent in order to be completed, and IRB approval was obtained from Newman University. The research question, investigating whether the use of Exparel provided better postoperative pain control with less opioid consumption was better understood by the results of the research articles. Descriptive statistics were used to compare and analyze the information found within the research articles. Descriptive statistics are useful in describing the features of the data obtained within a research article.

**Summary**

The researchers conducted a systematic review in order to determine whether the use of Exparel as an ILI would provide better postoperative pain control, decrease opioid requirements, and shorten hospital stay when compared to an ISBPB with Bupivacaine HCl. A systematic review was chosen to compare multiple studies and increase the study population size. The newness of the drug Exparel along with its limited use reinforces the need for this study and its findings. The information provided by this study could benefit anesthesia providers offering pain relief to patients undergoing TSA.
Chapter 4

Introduction

Postoperative pain control is of great importance to the patient undergoing a TSA. The best regimen to provide this pain control is a highly debated topic with many different options available. Regional anesthesia with local anesthetics has long been understood to improve postoperative pain scores and overall patient satisfaction scores while decreasing hospital stay, time to ambulation, and overall opioid consumption. The ISBPB is a common regional blockade added to the anesthetic plan for patients undergoing procedures on the shoulder and upper extremity. Although effective at providing pain relief following these procedures, the ISBPB is not without possible complications. Instances of a failed block are reported in 10-20% of patients, along with the potential for nerve damage, hemodynamic changes from the Bezold-Jarisch reflex, and a phenomenon known as rebound pain that results in higher pain scores when compared to patients not receiving ISBPB for TSA. Some surgeons prefer to use the method of ILI using a cocktail of medications to provide extended pain relief. The recently FDA approved drug Exparel is a liposomal form of the local anesthetic Bupivacaine. The manufacturers of Exparel have reported that it provides pain relief up to 72 hours following surgery. The researchers in this study performed a systematic review of the literature to determine whether opioid consumption, postoperative pain scores, and length of hospital stay differed between groups of patients undergoing a TSA who received an ISBPB vs ILI of Exparel.

Characteristics of the Sample
To perform a systematic review, the researchers utilized an online database search with the keywords of total shoulder arthroplasty, slow release bupivacaine, liposome bupivacaine, Exparel, interscalene, and brachial plexus block. The primary inclusion criteria for this systematic review was that patients must have undergone TSA or reverse TSA where ILI of Exparel versus preoperative ISBPB was utilized for the primary method of postoperative pain reduction. Using this criteria, the researchers obtained four prospective randomized control trials and two retrospective chart reviews that provided 493 patients who underwent a TSA from the years of 2012-2016. Patients were not excluded from this systematic review based upon ASA-physical status, patient age, patient gender, specific dosages of medications, or cocktail of medications utilized in the ILI or ISBPB. However, this data is reported in table 1 for completeness.
#### Table 1: Demographics

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Participants</th>
<th>Mean age</th>
<th>Male</th>
<th>Female</th>
<th>BMI (if included)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namdari et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>78</td>
<td>70.9</td>
<td>40</td>
<td>30.1</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>78</td>
<td>68.4</td>
<td>31</td>
<td>31.0</td>
</tr>
<tr>
<td>Okoroha et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>31</td>
<td>67.1</td>
<td>16</td>
<td>29.8</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>26</td>
<td>69.4</td>
<td>12</td>
<td>33.2</td>
</tr>
<tr>
<td>Angerame et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>44</td>
<td>68.8</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>25</td>
<td>66.0</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Sebesan et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>36</td>
<td>65</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>34</td>
<td>63</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Abildgarrd et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>46</td>
<td>-</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>37</td>
<td>-</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Hannan et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>ISBPB</td>
<td>21</td>
<td>63</td>
<td>9</td>
<td>28.8</td>
</tr>
<tr>
<td></td>
<td>ILI</td>
<td>37</td>
<td>65</td>
<td>17</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Data was collected from these six studies and organized into charts respectively for mean VAS pain scores at 0, 6, 12, 24, and 48 hours (Table 2), total postoperative opioids (Table 3), and length of hospital stay (Table 4). The data presented on Table 2 shows that VAS pain scores were lower in the ISBPB group upon arrival in the PACU in 5 out of 6 studies. Average VAS pain scores at PACU arrival were 1.86 in the ISBPB groups and 4.13 in the ILI groups. At 12 hours, the data showed little difference in pain scores between the two groups with the average VAS pain score being a 4.04 in the ISBPB groups and a 4.18 in the ILI groups. Some difference
was seen at 24 hours with the ILI group having lower scores at an average of 3.81 versus the ISBPB group at 4.89. This trend continued at 48 hours with the ILI group being lower again at an average of 4.48 versus the ISBPB group at 6.55. Table 3 examines the total morphine equivalents consumed by patients in the first 24 hours following surgery. The average for the ISBPB groups was less at 56.1 mg versus 67.9 mg in the ILI group. Table 4 shows that the length of hospital stay for both groups had very little variation with the ISBPB group staying an average of 1.91 days compared to the ILI at 1.81 days.
<table>
<thead>
<tr>
<th>Author</th>
<th>0 hours</th>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namdari et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>0.8 (±2.2)</td>
<td>1.4 (± 2.4)</td>
<td>4.3 (± 2.8)</td>
<td>4.9 (± 2.7)</td>
<td>-</td>
</tr>
<tr>
<td>Ili</td>
<td>3.3 (±2.7)</td>
<td>3.2 (± 2.2)</td>
<td>3.8 (± 2.4)</td>
<td>3.9 (± 2.3)</td>
<td>-</td>
</tr>
<tr>
<td>Okoroha et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>2.5 (± 3.0)</td>
<td>2.5 (±2.8)</td>
<td>3.7 (±3.1)</td>
<td>5.4 (±2.1)</td>
<td>4.0 (±1.8)</td>
</tr>
<tr>
<td>Ili</td>
<td>5.3 (±2.2)</td>
<td>4.9 (±2.3)</td>
<td>5.0 (±2.6)</td>
<td>4.5 (±2.5)</td>
<td>4.7 (±2.3)</td>
</tr>
<tr>
<td>Angerame et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>-</td>
<td>4.41</td>
<td>4.89</td>
<td>4.76</td>
<td>4.19</td>
</tr>
<tr>
<td>Ili</td>
<td>-</td>
<td>3.01</td>
<td>5.20</td>
<td>4.66</td>
<td>4.90</td>
</tr>
<tr>
<td>Sebesan et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>1.1 (±2.7)</td>
<td>1.5 (±2.6)</td>
<td>2.7 (±3.4)</td>
<td>2.9 (±3.0)</td>
<td>3.2 (±3.3)</td>
</tr>
<tr>
<td>Ili</td>
<td>0.8 (±2.1)</td>
<td>1.4 (±2.6)</td>
<td>2.1 (±3.0)</td>
<td>2.0 (±2.7)</td>
<td>2.6 (±3.0)</td>
</tr>
<tr>
<td>Abildgarrd et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>1.91</td>
<td>3.20</td>
<td>4.99</td>
<td></td>
<td>4.99</td>
</tr>
<tr>
<td>Ili</td>
<td>7.25</td>
<td></td>
<td>4.99</td>
<td></td>
<td>5.21</td>
</tr>
<tr>
<td>Hannan et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>3</td>
<td>5.5</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ili</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISBPB</td>
<td>1.86</td>
<td>2.35</td>
<td>4.04</td>
<td>4.89</td>
<td>6.55</td>
</tr>
<tr>
<td>Ili</td>
<td>4.13</td>
<td>3.12</td>
<td>4.18</td>
<td>3.81</td>
<td>4.48</td>
</tr>
</tbody>
</table>
### Table 3: Total Morphine Equivalents in 24 hours

<table>
<thead>
<tr>
<th>Author</th>
<th>ISB PB</th>
<th>Exparel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namdari et al(^1)</td>
<td>23.4 (± 12.7)</td>
<td>30.8 (± 18.5)</td>
</tr>
<tr>
<td>Okoroha et al(^9)</td>
<td>21.4 (± 11.3)</td>
<td>14.8 (±9.2)</td>
</tr>
<tr>
<td>Angerame et al(^{13})</td>
<td>123 (± 50)</td>
<td>134 (± 60)</td>
</tr>
<tr>
<td>Sebesan et al(^{14})</td>
<td>33.5</td>
<td>35.5</td>
</tr>
<tr>
<td>Abildgarrd et al(^{15})</td>
<td>15.04</td>
<td>32.64</td>
</tr>
<tr>
<td>Hannan et al(^{16})</td>
<td>120</td>
<td>160</td>
</tr>
<tr>
<td><strong>Average:</strong></td>
<td>56.05</td>
<td>67.9</td>
</tr>
</tbody>
</table>

### Table 4: Length of Hospital Stay (days)

<table>
<thead>
<tr>
<th>Author</th>
<th>ISB PB</th>
<th>Exparel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namdari et al(^1)</td>
<td>1.8 ± 0.6</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>Okoroha et al(^9)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Angerame et al(^{13})</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Sebesan et al(^{14})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abildgarrd et al(^{15})</td>
<td>1.87</td>
<td>1.95</td>
</tr>
<tr>
<td>Hannan et al(^{16})</td>
<td>2.38 (± 0.5)</td>
<td>1.91 (± 0.8)</td>
</tr>
<tr>
<td><strong>Average:</strong></td>
<td>1.91</td>
<td>1.81</td>
</tr>
</tbody>
</table>

### Results

The purpose of this systematic review was to determine which method provided greater relief of pain following TSA. The researchers outlined three research questions that can now be evaluated and answered based upon the findings. After an extensive review of the literature was performed the researchers have determined that postoperative opioid consumption is not reduced in the patients who receive only an ILI of Exparel for postoperative pain control. Infact, five out of six studies included in this review reported increased opioid consumption for the ILI group. No significant difference between either group was discovered when comparing VAS pain scores at 0, 6, 12, 24, and 48 or hospital length of stay following TSA.

### Summary
With recent FDA approval and claims of Exparel providing postoperative pain relief to patients for up to 72 hours the researchers hypothesized that the use of Exparel as an ILI would reduce the overall requirements of postoperative opioids, decrease VAS pain scores, and decrease hospital LOS. After performing an extensive review of the literature the researchers discovered that Exparel has not been shown to provide superior pain control following major shoulder surgery when compared the the ISBPB. Based upon the VAS pain scores and LOS comparison, it could be suggested that ILI of Exparel can be used effectively for postoperative comfort. However, evidence from the literature did not support the claim that ILI of Exparel would extend pain relief up to 72 hours or reduce the use of postoperative opioids.
Chapter 5

Introduction

The study consisted of a systematic review in an effort to compare the effectiveness of two regional anesthesia methods which include ISBPB with Bupivacaine HCl only and ILI of liposomal bupivacaine (Exparel). Six primary studies were examined spanning from years 2012 to 2016. The studies which were reviewed included patients undergoing TSA receiving regional anesthetic blockade with either Exparel or Bupivacaine HCl. The dependent variables examined in the study include postoperative pain scores, postoperative opioid consumption, and length of hospital stay. Postoperative pain scores were measured at 0, 6, 12, 24, and 48 hours. The purpose of this study was to determine whether or not the addition of Exparel to regional anesthesia provides better postoperative pain relief to patients undergoing TSA and decreased the length of hospital stay.

Interpretation of Findings

The systematic review was carried out by examining 6 studies comparing the effectiveness of Exparel to Bupivacaine HCl in TSA. The researchers primary interest was data comparing postoperative pain scores, postoperative opioid consumption, and length of hospital stay. Exparel was evaluated for superiority in decreasing all three variables. The result of this review revealed that Exparel is not statistically superior to Bupivacaine HCl in postoperative opioid consumption, postoperative pain scores, or length of hospital stay. It was revealed that Exparel and Bupivacaine HCl were statistically equal in postoperative pain scores and hospital
length of stay in patients who underwent TSA. However, some data did point to higher opioid consumption in the patients receiving Exparel as an ILI.

**Inferences about the Important Findings**

The primary findings of the study concluded that the use of Exparel is equivalent to the use of Bupivacaine HCl in providing postoperative pain relief and decreasing opioid consumption following TSA. There was also no statistical difference noted in the length of hospital stay. This is significant information for anesthesia practitioners with the high popularity Exparel has gained in regional anesthesia. It is believed that Exparel is the drug to use in regional anesthesia for a more dense and longer lasting regional nerve block. Namdari et al\(^3\) showed that total postoperative opioid consumption in the first 24 hours showed no difference between the two groups, and no significance was determined in the length of hospital stay between the two groups. The reasoning for the current study is the uncertainty about the efficacy of Exparel in providing better postoperative pain relief, lower postoperative opioid consumption, and decreased length of hospital stay when compared to Bupivacaine HCl. Moreover, Okoroha et al\(^9\) discovered no significant difference in VAS pain scores, opioid consumption, or hospital length of stay between the two groups after the day of surgery.

There was a need for research providing a better comparison between Exparel and a local anesthetic such as Bupivacaine HCl. Each article listed in the study compared Exparel equally with Bupivacaine HCl. The study examined articles of high reliability and low bias to formulate an evidenced based opinion about the effectiveness of ILI with Exparel. This makes the study a
valid contribution to the current body of literature regarding the use of Exparel in regional anesthesia for TSA.

**Implications**

The implications of the study include furthering education and providing better care through evidence-based practice. The findings can be used in future education surrounding the topic of using Exparel in regional anesthesia for total shoulder arthroplasties. The results suggest that Bupivacaine HCl provides parallel analgesia when compared to Exparel when used in regional anesthesia for TSA. These results give anesthetists sufficient knowledge when determining which drug to use when providing regional anesthesia for TSA. These results are important due to the fact that Exparel is a new drug and has gained wide popularity in regional anesthesia. A 133 mg (10 mL) vial of Exparel costs $175, whereas a 250 mg (50 mL) vial of bupivacaine HCl costs $3.72. With the results of the current study, along with drastic difference in price, researchers can now recommend the beneficial use of Bupivacaine HCl over Exparel. It is reasonable to say that using Exparel does not provide added benefit to patients receiving regional anesthesia for TSA. Additionally, the claims of Exparel providing reduced pain scores out to 72 hours postoperatively, as the manufacturer claims, is not duplicated in any study examined in this systematic review.

**Recommendations**

According to the results of the study, the authors recommend the use of Bupivacaine HCl over ILI with Exparel in regional anesthesia for TSA. It has become apparent throughout the study that Bupivacaine HCl provides equivalent postoperative analgesia for patients undergoing
TSA, which is supported by a lack of statistical difference in postoperative pain scores, postoperative opioid consumption, and length of hospital stay. This evidence not only challenges Exparel’s beneficial claims, but also discourages anesthesia providers from using the product.

The authors recommend that future research on this topic include peripheral nerve blocks covering different regions of the body for different surgical procedures. To allow for more consistent comparison in future studies the authors would suggest that Exparel be administered via targeted peripheral nerve block versus ILI. Research should include the comparison of the same local anesthetics with large sample groups of patients with varying ages and backgrounds. Patients would be chosen for one of the two groups through random selection to maintain validity. The authors also recommend that patients receive the peripheral nerve blocks and procedures from a variety of anesthesia providers and surgeons. Additionally, a consideration for future research would include predetermined times and methods of collecting postoperative pain scores. Patients could be given paper surveys composed of a visual analogue scale and specific pain related questions. This would potentially allow for truthful responses by patients and unbiased survey collection and interpretation.

Summary

It has been determined, through a systematic review, that Exparel and Bupivacaine HCl are statistically equal when comparing postoperative pain relief, postoperative opioid consumption, and length of hospital stay for patients undergoing TSA. The current study argues against the claim that Exparel is superior in providing a longer lasting and more dense peripheral nerve block when compared to Bupivacaine HCl. This study adds to the existing body of
knowledge surrounding Exparel and its uses in regional anesthesia. However, there are still many opportunities for further research on this topic.
References


December 17, 2018

Dear Dr. Lugo-Baez:

I have reviewed your proposed research project “Intraoperative Local Infiltration of Exparel versus Interscalene Brachial Plexus Block for Postoperative Pain Control in Total Shoulder Arthroplasty” and believe it to be exempt from further review by the Newman University Institutional Review Board under the Code of Federal Regulations, Title 45 HHS Part 46, Section 46.101(b)(2). Please keep a copy of this document with your records for at least 3 years following the conclusion of your proposed research project. Additionally, you agreed to maintain raw data for a minimum of three years beyond the completion of the study.

Thank you for your help in this matter, and please do not hesitate to contact me (please reference the code NL121718A) if you have any further questions. I would appreciate it if you would notify your co-investigators, Matt Merrill and Jacob Palmer, of this decision as well.

Sincerely yours,

Lori Steiner, Ph.D.
Chair, Newman University Institutional Review Board
F: steinerl@newmanu.edu
T: 316.942.4291 ext 2263
I, David A. Money, hereby consent to serve on the following research committee, along with student researchers, Jacob Palmer, Matt Merrill, and Principal Researcher, Dr. Nancy Lugo-Baez, for their research project entitled: Intraoperative Local Infiltration of Exparel versus Interscalene Brachial Plexus Block for postoperative pain control in Total Shoulder Arthroplasty.

I understand that this responsibility includes meeting with the students and the rest of their committee periodically from now until their thesis is complete by their graduation in August 2019, to help guide them in their research, and production of the Handbook.

Furthermore, I understand that I will be expected to offer expert clinical advice with editorial critique of their study, at appropriate times, as their study progresses until its completion, and will return edits in a timely manner upon request.

I also agree to attend, if possible, the defense of their thesis. Dr. Nancy Lugo-Baez is the Principal Investigator. Please contact her at 316-9424291 ext. 2245, for any questions or concerns.

(Name and Credentials of Committee Member)  
(Date)
I, Sharon Niemann, hereby consent to serve on the following research committee, along with student researchers, Jacob Palmer, Matt Merrill, and Principal Researcher, Dr. Nancy Lugo-Baez, for their research project entitled: Intraoperative Local Infiltration of Exparel versus Interscalene Brachial Plexus Block for postoperative pain control in Total Shoulder Arthroplasty.

I understand that this responsibility includes meeting with the students and the rest of their committee periodically from now until their thesis is complete by their graduation in August 2019, to help guide them in their research, and production of the Handbook.

Furthermore, I understand that I will be expected to offer expert clinical advice with editorial critique of their study, at appropriate times, as their study progresses until its completion, and will return edits in a timely manner upon request.

I also agree to attend, if possible, the defense of their thesis. Dr. Nancy Lugo-Baez is the Principal Investigator. Please contact her at 316-942-4291 ext. 2245, for any questions or concerns.

Sharon Niemann, ONA, CRNA

(Name and Credentials of Committee Member) (Date)