

Summer 2020

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Recommended Citation

Duraney, Jessica, "Exparel Versus Bupivacaine: Outcomes, Advantages, And Costs" (2020). *Nurse Anesthesia Capstones*. 38.

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Exparel versus Bupivacaine: Outcomes, Advantages, and Costs

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Abstract

Research shows that adequate pain control is associated with increased patient satisfaction, faster rehabilitation, mobilization, reduced hospital stays, and ultimately decreased hospital costs. Due to the many disadvantages of opioids, such as ileus, nausea, vomiting, respiratory depression, tolerance, and physical dependence, there has been a push for opioid-sparing and multimodal analgesia perioperatively. The purpose of this paper is to compare two local anesthetics, bupivacaine and Exparel (liposomal bupivacaine). The use of these drugs in various regional techniques, specifically for total knee arthroplasty (TKA) and abdominal surgeries, will be discussed.

Exparel versus Bupivacaine: Outcomes, Advantages, and Costs

The articles listed throughout this manuscript were found using the search engines CINAHL Complete, PubMed, and Google Scholar. The keywords utilized were regional anesthesia, Exparel, and liposomal bupivacaine.

Regional anesthesia is one way to limit opioid administration while still providing quality analgesia. With the advancements in ultrasound imaging over the past several years, regional anesthesia has become safer and more efficacious. Ultrasound allows the provider to visualize the target nerve directly and thus avoid accidental puncture of blood vessels and damage to nerves. Ultrasound usage has also been linked to shorter procedure times. The purpose of this research paper is to compare the use of bupivacaine to Exparel. Several outcomes will be considered including postoperative pain, opioid requirements, length of hospital stay (LOS), patient outcomes, and cost.

Bupivacaine

Bupivacaine is an amide local anesthetic. It works by decreasing the permeability of sodium ions through the neuronal membrane, thereby blocking the initiation and conduction of nerve impulses and inhibiting depolarization. Its onset of action is dependent on the route of administration. Contraindications to the use of bupivacaine include obstetrical paracervical blocks and Bier blocks. When infiltrated for peripheral nerve blocks, the onset of action is two to ten minutes and the peak time is thirty to forty-five minutes. Bupivacaine is 84-95% protein bound. It is metabolized via the liver. The half-life of bupivacaine is age-dependent ranging from 2.7 hours in adults to 8.1 hours in neonates. Bupivacaine is excreted via the urine (Bupivacaine: Drug information, n.d.).

The cost of Bupivacaine is variable based on specific concentrations and other additives. In a breast augmentation study conducted by Nadeau, Saraswat, Vasko, Elliott, and Vasko (2015), the cost of 20 mL of bupivacaine was \$1.15, compared to \$285 for 20 mL of liposomal bupivacaine.

Exparel (Liposomal Bupivacaine)

Exparel is a local anesthetic that uses DepoFoam drug delivery technology to encapsulate bupivacaine into multivesicular liposomes. Bupivacaine is released over time as the lipid membranes are reorganized in the human body (Exparel, 2019). The onset of Exparel is rapid. The duration of action is up to 72 hours, however systemic plasma levels can persist for 96 hours after administered locally, and 120 hours after administered into the brachial plexus for an interscalene nerve block. Exparel peaks twice. The initial peak is at one hour and the second peak occurs at 12 to 36 hours. Exparel is 95% protein-bound and is metabolized primarily via hepatic conjugation, therefore it should be administered cautiously to patients with hepatic disease. It is excreted via the urine. The elimination half-life is 13-34 hours (Liposomal Bupivacaine: Drug Information, n.d.).

Exparel has been approved for single-dose infiltration for postsurgical local analgesia in adults and interscalene brachial plexus nerve blocks. It has not yet been approved for other nerve blocks. Exparel should not be administered with other local anesthetics because bupivacaine may be immediately released leading to a higher potential for toxicity. It is safe to inject Exparel twenty minutes after lidocaine has been administered into the same location. Other forms of bupivacaine should not be administered within 96 hours of the administration of Exparel (Change the face of postsurgical recovery, 2019). To maintain Exparel's structural integrity, no needle smaller than 25 gauge should be used for administration (Exparel, 2019).

Exparel is contraindicated in paracervical blocks in obstetric patients. It is not recommended for use in patients under eighteen years old, or in pregnant patients due to the risk of fetal bradycardia and death. Exparel is not recommended for epidural, intrathecal, intravascular, intra-articular use, or regional nerve blocks other than interscalene brachial plexus blocks. It is currently being researched in several other surgeries including bariatric, breast, colorectal, general, obstetrics and gynecology, oral and maxillofacial, orthopedic, and spine. Adverse central nervous system (CNS) effects that can occur following Exparel administration include unconsciousness, respiratory arrest, and convulsions. Signs of CNS toxicity include restlessness, incoherent speech, circumoral numbness and tingling, metallic taste, twitching, tinnitus, blurred vision, dizziness, and drowsiness. Toxic concentrations can lead to cardiovascular changes including decreased cardiac output, hypotension, atrioventricular block, ventricular arrhythmias and cardiac arrest (Liposomal Bupivacaine: Drug Information, n.d.). The current cost of Exparel is listed as \$21.01 per mL (1.3%) (Liposomal Bupivacaine: Drug Information, n.d.).

Literature Review

The use of liposomal bupivacaine in periarticular injections

Schroer, Diesfeld, LeMarr, Morton, and Reedy (2015)

Local anesthetics can be injected around joints for analgesia. Periarticular blocks are advantageous because the surgeon can administer them intraoperatively, with no extra step required. Research has shown that by blocking pain receptors at the location of injury central sensitization can be avoided. Schroer, Diesfeld, LeMarr, Morton, and Reedy (2015) conducted a Level II prospective, randomized controlled trial involving 111 patients undergoing unilateral total knee arthroplasty (TKA). The study group consisted of fifty-eight patients who received

266 mg (20 mL) of liposomal bupivacaine (LB) with 75 mg (30 mL) of 0.25% bupivacaine via periarticular injection (PAI). The control group consisted of fifty-three patients who received 150 mg (60 mL) of 0.25% bupivacaine via PAI. Spinal anesthesia was administered to both groups and consisted of 25 mcg fentanyl and 2 mL of 0.75% bupivacaine, followed by propofol for conscious sedation. Throughout the surgery 8 mg of dexamethasone, 8 mg ondansetron, and 10 mg/kg of tranexamic acid (up to 1 gram) were administered. During the postoperative period, patients received 400 mg celecoxib daily and 20 mg OxyContin every 12 hours for 2 doses. Patient-Controlled analgesia (PCA) pumps delivering hydrocodone, oxycodone, and morphine were available for breakthrough pain.

Results

Primary measures of this study were pain scores obtained using the Visual Analog Scale (VAS). Secondary outcomes included length of hospital stay (LOS), knee flexion at discharge, knee flexion at three weeks, and narcotic use during hospitalization. The results of this study showed that pain scores were similar between both groups. On the morning of postoperative day (POD) 1 pain scores were 4.5 for the study group and 4.6 for the control group, ($p = .73$). On the afternoon of POD 1, pain scores were 4.1 and 4.5, ($p = .28$). On the morning of POD 2, pain scores were 4.4 and 4.8, ($p = .27$). On the afternoon of POD 2, pain scores were 4.1 and 4.6, ($p = .23$). On the morning of POD 3, pain scores were 3.9 and 4.1, ($p = .57$). The length of hospital stay was 2.9 for the study group versus 3.0 for the control group, ($p = .98$). At discharge, knee ROM was 81 degrees (study group) compared to 77 degrees (control group), ($p = .14$). Three weeks following surgery knee ROM was 107 degrees (study group) and 108 degrees (control group), ($p = .47$). Narcotic requirements were slightly lower in the study group (51.8) compared to the control group (54.2), ($p = .34$). Five percent of patients in the study group experienced

postoperative nausea versus four percent in the control group, ($p = .72$) (Schroer, Diesfeld, LeMarr, Morton, and Reedy, 2015).

The results of this study showed no substantial benefit of LB versus bupivacaine in periarticular injections for TKA. The use of LB did not result in improved pain scores, reduced narcotic use, or enhanced knee ROM during the hospital stay. Considering the results and the large cost difference between Exparel (\$285) and bupivacaine (\$2.80), the authors do not support the routine use of LB (Schroer et al., 2015).

Limitations

Several limitations exist in this study. The surgeon and the surgical team were not blinded to the technique used. Another limitation was the size of the study population. More than 1000 patients are needed to attain a greater than or equal to 0.2 VAS difference (Schroer et al., 2015).

Liu et al. (2019)

Liu et al. (2019) conducted a Level I meta-analysis of thirteen randomized controlled trials (RCTs) that examined liposomal bupivacaine (LB) to traditional PAIs. Traditional PAIs consisted of bupivacaine and a cocktail of either ropivacaine, epinephrine, ketorolac, or clonidine. The LB group consisted of 691 patients. The traditional PAI group included 682 patients. The primary outcome of this study was postoperative pain using VAS. Secondary outcomes included opioid consumption (morphine equivalents), LOS, and adverse effects. The Cochrane Collaboration tool was utilized to assess bias risk.

Results

The results of this study showed that postoperative pain using the VAS, at every period following TKA, was similar between both groups. During the first 24 hours following TKA, the

LB group had similar pain scores compared to the traditional PAI group, ($p = .09$). Pain scores during the second twenty-four hours following TKA were similar between both groups, ($p = .12$). Pain scores in the third twenty-four hours following TKA were similar between both groups, ($p = .12$). During the first twenty-four hours following TKA results showed that the LB group did not consume significantly fewer opioids compared to the traditional PAI group, ($p = .45$). During the second twenty-four hours following TKA, the LB group consumed significantly fewer opioids compared to the traditional PAI group, ($p = .01$). During the third twenty-four hours following TKA, the LB group also consumed significantly fewer opioids compared to the traditional PAI group, ($p = .006$). The rates of postoperative nausea and vomiting (PONV) were lower in the LB group compared to the traditional PAI group, ($p = .05$), however, significance was not reached. LOS was not significantly longer in the LB group, ($p = .50$) (Liu et al., 2019).

Limitations

The first limitation was that not all of the RCTs included in this meta-analysis examined all outcomes. Therefore, the analysis only included a small sample. The authors explain that the RCTs could have been of better quality and more relevant to provide more worthwhile results. The various cocktails used amongst the different groups could have influenced the results. The last limitation mentioned was that functional recovery was not assessed amongst the groups. The authors recommend that future studies should focus on the most effective drug composition for periarticular injections. The same periarticular injection technique should be confirmed throughout all groups to reduce bias (Liu et al., 2019).

Wang, Xiao, Wang, Zhao, and Ma (2017)

Wang et al. (2017) conducted a Level I systemic review and meta-analysis comparing bupivacaine to liposomal bupivacaine in terms of safety and efficacy following TKA. Ultimately,

three RCTs and two Non-RCTs were included in this meta-analysis. Three studies used spinal anesthesia. The other studies used general anesthesia.

Results

Throughout 72 hours following surgery pain was reduced in the LB group (141.8) versus 202.5 ($p < 0.0001$). Opioid consumption (morphine equivalents) on POD 1 were significantly higher in the control group. Opioid consumption was similar between both groups on POD 2 and 3. On POD 1, significantly fewer opioids were needed in the group that received a LB-based multi-modal pain regimen (20 mg) than the bupivacaine group (112 mg), ($p < 0.01$). The LB group experienced lower rates of PONV. Ultimately, the findings presented within this meta-analysis demonstrated that LB provided superior pain relief, decreased opioid consumption, and fewer side effects compared to periarticular injections of traditional bupivacaine (Wang, et al., 2017).

Limitations

Only five studies, with small sample sizes, were included in this meta-analysis. Functional outcomes were not considered due to scarce data. Anesthetic doses and pain management regimens were not standard throughout the studies. Another limitation of this study was a short follow-up period. The authors mention that in future studies the combined use of epinephrine, NSAIDs, and femoral nerve block (FNB) should be studied (Wang et al., 2017).

Kuang et al. (2017)

Kuang et al. (2017) conducted a Level I systematic review and meta-analysis comparing pain relief and functional recovery after TKA between patients who received Exparel via periarticular injection versus placebo or actual bupivacaine hydrochloride. Eleven studies were included in this meta-analysis. Four were RCTs, and seven were non-RCTs. The primary

outcome was VAS scores. The secondary outcome was opioid consumption (morphine equivalents) during hospitalization. Other outcomes examined included ROM, LOS, PONV, and ambulation distance.

Results

Results showed that liposomal bupivacaine provided similar VAS scores at 24 hours ($p = .46$), 48 hours ($p = .43$), and 72 hours ($p = .21$). Both groups also had similar total opioid consumption ($p = .25$), ROM ($p = .28$), LOS ($p = .53$), PONV ($p = .34$), and ambulation distance ($p = .07$). The authors of this study ultimately do not consider liposomal bupivacaine worthy, due to the significant cost difference (Kuang et al., 2017).

Limitations

Only four RCTs were included in this meta-analysis. To increase the statistical value more should be included. The authors recommend longer follow-up periods in the future. Several potential causes of heterogeneity exist including variable liposomal bupivacaine dosages, anesthetic technique, PAI method, and the tourniquet (Kuang et al., 2017).

Schwarzkopf et al. (2016)

Schwarzkopf et al. (2016) conducted a Level III, comparative study including thirty-eight patients. The goal of this study was to determine whether or not LB resulted in better outcomes in patients with a history of chronic opioid use, compared to traditional PAIs. All patients had unilateral cemented TKA and resurfaced patella, through a medial parapatellar approach, performed by the same surgeon and technique. Patients were randomly assigned to either receive PAI with LB ($n = 20$) or standard PAI combination of ropivacaine, clonidine, ketorolac, epinephrine and saline ($n = 18$). Patients in the LB group received 20 mL of liposomal bupivacaine, 60 mL of saline, and 20 mL of 0.25% bupivacaine. Patients in the standard PAI

group received 0.5% ropivacaine (49.25 mL), 80 mg clonidine (0.8 mL), 30 mg Toradol (1 mL), 0.5 mg epinephrine (0.5 mL), and 48 mL of saline.

Results

Since patients with chronic pain have different narcotic tolerances baseline narcotic usage was considered preoperatively. Throughout the study postoperative narcotic use, average daily pain scores, and maximum daily pain scores were similar between both groups. When examining daily VAS scores separately, the LB group experienced higher scores in POD 1. There was no significant difference in first time opioid use in the recovery room between the LB group (4 minutes) and the control group (24 minutes), ($p = .2365$). LOS was similar between both groups ($p = .91$). Ultimately LB was not found to be superior. The results of this study did not justify the increased cost (Schwarzkopf et al, 2016).

Limitations

This study could be improved with larger prospective trials. Another limitation of this study is the vastly different techniques used for periarticular injections. The authors suggest in the future that outcomes from several surgeons will help reduce bias in technique (Schwarzkopf et al., 2016).

Smith et al. (2017)

Smith et al. (2017) conducted a Level I double-blinded, RCT. The purpose of this study was to examine the outcomes associated with intraarticular bupivacaine hydrochloride via infusion catheters (ON-Q) versus periarticular injections of Exparel. Ninety-six patients were part of the ON-Q group. One hundred four patients were part of the Exparel group. The Exparel group received 266 mg LB (20 mL) and normal saline (40 mL). The primary outcome was

cumulative narcotic consumption on POD 0-3. This data was retrospectively gathered from hospital records. Once discharged, data was collected via patient surveys.

Results

Opioid consumption was gauged using morphine equivalents. On POD 0-3 the ON-Q group consumed, on average, 10.4 morphine equivalents compared to the Exparel group that averaged 10.9. This finding was not significant, ($p = .641$). On POD 0-3 patients in the ON-Q group rated their pain 3.6. The Exparel group rated their pain, on average, 4.0. This finding was insignificant, ($p = .373$). The maximum and minimum pain scores were similar between both groups on all postoperative days. The Exparel group reported that pain interfered with their ability to walk (4.6 points) more than the ON-Q group (3.5 points), ($p = .019$), which made this finding significant. Pain significantly impacted the Exparel group more (4.5 points) than the ON-Q group (3.2 points), ($p = .010$). Twenty-two percent of patients in the ON-Q group suffered from bleeding or leakage around the pump. Due to this complication, five percent of the ON-Q group required catheter removal. Three percent of patients in the Exparel group required manipulation of the knee due to stiffness at 57 and 70 days postop, compared to five percent in the ON-Q group. There were no differences in LOS, patient satisfaction, complications, PONV, or constipation in either group. According to the authors of this study, Exparel was not proven to be superior to ON-Q. It is suggested that further research is needed to examine the complication rates and costs associated with continuous catheter infusions (Smith et al., 2017).

Limitations

Senior surgeons were to remain blinded, therefore they were unable to perform the injections. Although surgical assistants were trained regarding the proper way to administer Exparel, variations are possible. Exparel was not injected until after the site was closed, therefore

it was not possible to inject into the posterior of the capsule or the periosteum. This could lead to adverse results in the Exparel group. Another limitation was that long-term results were not acquired. The Exparel group had an imitation pump attached to their lower extremity, to remain blind. This could have possibly masked the mobility and comfort in the Exparel group. Lastly, to achieve the desired power of 0.8, 238 patients were needed for this study. This study only enrolled 200 patients (Smith et al., 2017).

Alijanipour et al. (2017)

A Level I RCT was conducted by Alijanipour et al. (2017) to compare liposomal bupivacaine (experimental group) to bupivacaine (control group). 162 patients who underwent primary TKA between January 2014 and May 2015 were included in this study. Seventy-five patients were randomly assigned to the control group and eighty-seven patients were assigned to the experimental group. Patients in the experimental group received 266 mg (20 mL) of liposomal bupivacaine with 40 mL of sterile normal saline and 0.5 mg epinephrine (0.5 mL). The control group received 50 mg of 0.25% bupivacaine (20 mL) with 1:200,000 epinephrine. This solution was diluted with 40 mL of normal saline. Postoperatively, all patients received identical surgical techniques, spinal anesthesia, pain management, and rehabilitation. The primary outcome of this study pain scores via VAS 96 hours postop. Secondary outcomes included opioid consumption (morphine equivalents), opioid-related side effects, patient satisfaction during the first 96 hours following surgery. Functional outcomes and complications were also evaluated.

Results

Preoperatively, the experimental group reported lower rates of average daily pain. The results of this study showed no differences in the least, worst, and average pain in either group.

Both groups experienced an increase in pain 6-12 hours postoperatively. After the peak, the control group did not experience a decline in pain until the morning of POD 2. There were no statistically significant differences between either group regarding postoperative pain scores on each day, opioid consumption (daily and overall), opioid-related side effects, surgical or medical complications, LOS, or patient satisfaction. Exparel did not result in improved outcomes (Alijanipour et al., 2017).

Limitations

Pain assessments were completed at 8 am and at 5 pm, regardless of the time of the surgical procedure, physical therapy, or administration of pain medication. These factors could have potentially influenced pain scores. The surgeons were not blinded while administering the medication. After reviewing the findings, it was discovered that two patients did not meet inclusion criteria. One patient in the experimental group had a history of opioid addiction. One patient in the control group had many knee surgeries twenty years before this study regarding TKA (Alijanipour et al., 2017).

Jain et al. (2016)

Jain et al. (2016) conducted a single-blinded, prospective, randomized study to examine outcomes between three groups, all undergoing TKA. Arm 1 consisted of patients who received intra-articular injections of 0.25% bupivacaine (30 mL) with epinephrine 1:200,000, and 10 mg of morphine at the end of the surgery. Arm 2 consisted of periarticular injections of 0.25% bupivacaine with epinephrine 1:200,000, and 10 mg of morphine. Arm 3 received a periarticular injection of liposomal bupivacaine. Primary outcomes included average postoperative pain ratings for the entire hospital stay (using Wong-Baker pain faces scale). Secondary outcomes

included average in-hospital opioid intake (using morphine equivalents) and the cost of pain medications during hospital stay (perioperative and postoperative).

Results

There were no significant differences in average or maximum postoperative pain scores in either group. No significant differences were seen in morphine equivalents postoperatively. LOS in days were as follows: 1.3 (Arm 1), 1.2 (Arm 2), and 1.4 (Arm 3), ($p = .09$). Maximum pain scores were as follows: 5.85 (Arm 1), 5.81 (Arm 2), and 5.69 (Arm 3), ($p = .92$). Average pain scores were as follows: 3.95 (Arm 1), 3.97 (Arm 2), and 3.86 (Arm 3), ($p = .94$). Mean morphine equivalents (MME) per 24 hours were as follows: 100.7 (Arm 1), 100.1 (Arm 2), and 98.9 (Arm 3), ($p = .97$). The average cost of perioperative and postoperative pain management was significantly higher in Arm 3 (LB group) at an average of \$402.09. Arm 1 totaled \$15.99 and Arm 2 totaled \$23.21. The authors concluded that there was no benefit regarding the outcome or cost when using LB. An intraarticular injection of bupivacaine with morphine was proven to be as effective and required less time (Jain et al., 2016).

Limitations

The nursing and physical therapy staff were the same for all patients, which could potentially lead to bias. The surgeon and OR team could not be blinded to the treatment but were not permitted to analyze or collect any data. The short LOS could have caused some positive outcomes associated with Exparel to go unnoticed. The manufacturer's recommendations for Exparel were followed and no other local anesthetics were used in conjunction. Several surgeons have noted that adding plain bupivacaine to Exparel allows for analgesia during the 8 to 12 hour period, while liposomal bupivacaine is not yet in full effect (Jain et al., 2016).

Mont, Beaver, Dysart, Barrington, and Del Gaizo (2018)

Mont et al. (2018) conducted a RCT comparing local infiltration of liposomal bupivacaine (LB) versus regular bupivacaine (without LB). Seventy patients received 266 mg liposomal bupivacaine (20 mL) and 0.5 % bupivacaine (20 mL) via local infiltration. Sixty-nine patients received 0.5% bupivacaine (20 mL) via local infiltration. Outcomes included pain, narcotic consumption, time to first narcotic rescue, the proportion of opioid-free patients, and safety.

Results

Average pain scores were significantly lower in the LB group (180.8) compared to the without LB group (209.3), ($p = .0381$). Total opioid consumption was significantly reduced in the LB group (18.7 mg) versus the without LB group (84.9 mg). Ninety percent of patients in the LB group required opioids, compared to 100% in the bupivacaine group. The time to first narcotic rescue was significantly longer in the LB (ranging from 0.25 to 48 hours) compared to 0.27 to 33 hours (without LB) group. Ultimately, LB was associated with improved postoperative pain, reduced opioid consumption, increased time before first narcotic rescue, and more opioid-free patients (Mont et al., 2018).

Limitations

The moderate size of this study can be considered a limitation. The only rescue medications that were used were opioids. If non-opioids were also utilized as rescue medications, opioid use could potentially be further reduced. Since all patients were required to stay in the hospital for two days, length of stay could not be examined. Another limitation to this study was the fact that healthcare costs and recovery time were not assessed (Mont et al., 2018).

Snyder, Scheuerman, Gregg, Ruhnke, and Eten (2016)

Snyder et al. (2016) organized a prospective, randomized, double-blind trial that compared postoperative pain scores in thirty-five patients who received liposomal bupivacaine (LB) versus thirty-five patients who received a concentrated cocktail injection in patients undergoing TKA. The liposomal bupivacaine group received 266 mg of bupivacaine with 0.9% normal saline (100 mL). The concentrated cocktail group received 30 mg ketorolac, 5 mg morphine, 0.6 mg epinephrine, 400 mg ropivacaine, and 0.9% normal saline (100 mL). Outcomes included post-op pain, opioid consumption (morphine equivalents), patient satisfaction with pain control, and adverse events. The surgeon responsible for the injection was blinded. Patients received either spinal anesthesia consisting of 0.75% ropivacaine or general anesthesia consisting of 1% propofol via a continuous infusion (Snyder et al., 2016).

Results

Patients in the LB group reported less pain in the PACU (2.68) compared to the concentrated cocktail group (2.87), ($p = .033$). Patients in the concentrated cocktail group experienced higher pain than the LB group, on POD 0, 1, and 2. Results could not be obtained on POD 3. Patients in the LB group required fewer narcotics in the PACU and on POD 0 through 2. Patient satisfaction was assessed using a 5 point Likert scale. Patients in the LB group experienced higher satisfaction with pain control while hospitalized (4.91 versus 4.11), ($p = .0001$). Overall pain satisfaction was also higher in the LB group (3.97 versus 4.57), ($p = .001$). Higher rates of nausea occurred in the concentrated cocktail group (19 versus 9), ($p = .011$). Ultimately, there was no significant difference in pain scores, opioid consumption, adverse effects, or patient satisfaction. There were fewer adverse events in the LB group (Snyder et al., 2016).

Limitations

Limitations of this study include the fact that postoperative pain scores cannot be generalized to all types of surgeries. Patients received different anesthesia techniques, neuraxial anesthesia versus general anesthesia, based on comorbidities. The authors of this study recommend that further research be completed to refine the differences in pain scores and patient satisfaction using various combinations of anesthesia and injection techniques (Snyder et al., 2016).

Zlotnicki et al. (2018)

A randomized, blinded, prospective study was conducted on 118 patients comparing periarticular injections of liposomal bupivacaine to plain bupivacaine. Primary outcomes included pain relief, total opioid use, completion of physical therapy goals, and ROM. Patients, nurses and physical therapists were blinded. Patients in the liposomal bupivacaine group received 30 mL of liposomal bupivacaine mixed with 70 mL of normal saline ($n = 38$). Patients in the bupivacaine group received 20 mL of 0.5% bupivacaine with 70 mL of normal saline ($n = 40$). The historical control group consisted of patients who did not receive periarticular injections but were enrolled in the preoperative and postoperative pain pathway ($n = 40$) (Zlotnicki et al., 2018).

Results

The LB group experienced decreased pain during physical therapy at 24 hours postop (5.4), compared to the control group (7.3) and the plain bupivacaine group (6.9). Both periarticular groups had significantly improved ROM. On POD 1 the LB group was able to flex 82.7 degrees, compared to 80 degrees in the plain bupivacaine group, and 66.4 degrees in the control group. Overall, LB did not result in significantly improved pain scores, ROM, or total

narcotic usage. Considering the cost difference of plain bupivacaine (\$2.28) compared to LB (\$282.72), the authors do not support the use of LB (Zlotnicki et al., 2018).

Limitations

The use of a historical control group allowed for the LB group and the plain bupivacaine group to be blinded, however it did not allow all groups to be prospective. Another limitation was that there was no power analysis or calculation of sample size before the study was implemented. Also, no post hoc power analysis was performed to eliminate biased results (Zlotnicki et al., 2018).

Bagsby, Ireland, and Meneghini (2014)

Bagsby et al. (2014) conducted a Level III retrospective cohort study to compare liposomal bupivacaine to traditional PAI for unilateral primary TKA. Eighty-five patients received a traditional PAI of ropivacaine, epinephrine, and morphine. Sixty-five patients received PAI of liposomal bupivacaine. All patients received single-shot morphine spinal preoperatively, light general anesthesia, as well as a periarticular injection of either ropivacaine, morphine, epinephrine, or LB. To provide analgesia during the immediate postoperative period, before LB was effective, the periarticular tissues were infiltrated with 0.5% bupivacaine with 1:200,000 epinephrine (30 mL). Postop pain scores were assessed every 2-4 hours using a VAS. The pain was also assessed at discharge. Patients received various doses of hydrocodone based on pain ratings. These values were then converted to opioid equivalents.

Results

Average pain scores from 24 hours postop until discharge were lower in the traditional group (4.4) compared to the LB group (4.9), which was statistically significant ($p = .04$). At discharge the pain scores were slightly higher in the traditional group (3.6) compared to 4.1 in

the LB group, this did not reach significance ($p = .14$). The results of this study did not show statistically different opioid requirements, average antiemetic requirements, or average naloxone doses. Ultimately, periarticular injections of LB resulted in inferior pain control at a higher expense. This could be due to the slow release of bupivacaine from the liposomes (Bagsby et al., 2014).

Limitations

The first limitation of this study was that it was not randomized. The second limitation deals with the technique used during periarticular injections which can potentially skew the results. Several nurses administered analgesics and antiemetics and documented them. The authors recommend that prospective, RCTs be conducted in the future (Bagsby et al., 2014).

Femoral nerve blocks with bupivacaine versus PAI using LB

Yu, Szulc, Walton, Bosco, and Iorio (2016)

Femoral nerve blocks (FNB) are commonly used for TKA surgeries but have been associated with quadricep weakness, and falls. Yu et al. (2016) conducted a Level III, therapeutic study comparing pain scores, narcotic use, mobilization, and in-hospital falls following 1,373 unilateral TKA surgeries. Two techniques were compared: femoral nerve blocks using bupivacaine ($n = 583$) and periarticular blocks using liposomal bupivacaine ($n = 527$). The FNB group received 0.25% bupivacaine (20 mL) and an intraoperative injection of 0.25% bupivacaine (40 mL), 5 mL morphine and 30 mg ketorolac (1 mL). The LB group received 20 mL of LB (260 mg) and 40 mL of normal saline.

Results

Throughout LOS, pain scores were similar between both groups. Overall, the LB group consumed fewer opioids through POD 2 ($p = .004$). Seventy-seven patients in the LB group were

able to ambulate 100 feet before discharge, compared to sixty percent in the FNB group ($p < .001$). Ninety-four percent of patients in the LB group were able to climb the stairs compared to seventy-three percent in the FNB group ($p < .001$). In-hospital falls were lower in the LB group (0.6%) compared to the FNB group (2%), ($p = .03$). The results of this study demonstrated that liposomal bupivacaine provides comparable pain control that allows for decreased narcotic use. It also eliminates the need for an additional procedure and risk of nerve injury, quadriceps weakness, and reduces the risk of falls. The authors of this study ultimately replaced FNBs with PAIs of LB for their TKA pain management protocol (Yu et al., 2016).

Limitations

The first limitation of this study was its retrospective approach. Another limitation was that it was historically controlled and the attrition bias was not corrected for. Lastly, twenty-four surgeons were involved in the administration of liposomal bupivacaine. Despite all surgeons receiving identical training, different techniques may have been used. The authors suggest that a large randomized trial be performed in the future (Yu et al., 2016).

Kirkness, Asche, Ren, Kim, and Rainville (2016)

Kirkness et al., (2016) organized a retrospective, single-site study involving 268 patients who underwent TKA. Two techniques were compared. The study group included patients who received Exparel via local infiltration during surgery ($n = 134$). The results were compared to a historical group that received a continuous femoral nerve block of bupivacaine via a pump between October 2011 and August 2013. The patients in the study group received 266 mg of liposomal bupivacaine (20 mL) combined with 30 mL of bupivacaine hydrochloride 0.25% and epinephrine. The patients in the historical cohort received 5 mg of hydrocodone bitartrate and 325 mg of acetaminophen preoperatively. This group also received one of the following

combinations: ketorolac 60 mg, 0.2% ropivacaine (60 mL), morphine sulfate 4 mg and epinephrine 0.2 mg or, ketorolac 15-30 mg and 0.25% bupivacaine with epinephrine (60 mL) or, ketorolac 30 mg, 0.2% ropivacaine (10 mL) and 0.2 mg epinephrine. In addition to these combinations, 0.2% ropivacaine (400 mL) was administered via a pump.

Results

The results of this study demonstrated that 22% of patients who received LB were able to walk on the day of surgery, compared to 3% who received a FNB ($p < .05$). Pain scores and opioid use during the postoperative period were similar in both groups however, the liposomal bupivacaine group required less nonsteroidal anti-inflammatory drugs. Fifty percent of the patients in the study group were discharged within two days of surgery compared to nineteen percent in the control group ($p < .001$). On average, patients in the study group were able to walk 6 meters on the day of surgery (DOS) compared to 3.1 meters in the control group ($p < .001$). On POD 1 the patients in the study group ambulated 53.7 meters compared to 25.5 meters (control group), $p < .001$). The average hospital length of stay was 3.1 days (study group) compared to 3.6 days (control group), $p < .03$. The most significant benefit of using LB was significantly lower costs. The mean adjusted total direct hospital cost per patient in the LB group was \$8,758 versus \$9,213 in the control group, a difference of \$455 ($p = .033$) (Kirkness et al., 2016).

Limitations

The results from a small medical center may not be generalized to a broader population. This study did not follow the manufacturer's recommendations during the preparation of Exparel. The third limitation was that this study analyzed its findings and compared them to a historical cohort of patients. Potential issues with retrospective electronic medical record (EMR) analyses include missing data such as diagnoses and adverse events, as well as coding errors. This study

used propensity score matching that took into account demographic and clinical characteristics, age, sex, body mass index (BMI), and race. However, it did not take into account improvements in recovery pathways that may have impacted the LOS. The last limitation was that safety outcomes were not assessed (Kirkness et al., 2016).

Singh et al. (2017)

A Level I meta-analysis was conducted by Singh et al. (2017) to evaluate the results of sixteen studies that took place over two years examining the results of periarticular liposomal bupivacaine for TKA. Primary outcome compared LOS. Secondary outcomes included analgesia requirements during the perioperative period, joint ROM, total perioperative opioid consumption, and postoperative pain scores. This meta-analysis compared several analgesic techniques such as knee infiltration of bupivacaine, femoral nerve block, multimodal systemic pain regimens, and other regional blocks (control groups), to immediate postoperative periarticular infiltration of LB into the knee joint (study group).

Results

In thirteen subgroups LB resulted in shorter LOS, compared to traditional TKA regimens including bupivacaine infiltration into the knee, femoral nerve block, multimodal regimens for systemic analgesia, and other regional blocks. Patients who received PAIs of Exparel had 0.17 +/- 0.04 days shorter LOS ($p < .001$). LB was associated with 0.21 points greater pain relief on POD 1, while compared to the other groups overall. When sub-grouped, pain scores in the LB group were statistically similar in the FNB group. On POD 2, those who received periarticular injections of liposomal bupivacaine had better pain scores by 0.23 points. LB could not be analyzed regarding whether it reduced total opioid consumption and increased ROM because the sample size was too small. Overall, the infiltration of liposomal bupivacaine slightly shortens

LOS, especially compared to femoral nerve blocks. When compared to other analgesic therapies listed in this meta-analysis, liposomal bupivacaine provides marginally superior but sustained pain relief throughout POD 2. Although the price of LB is approximately \$300 compared to bupivacaine (\$2.50 to \$8), three studies within this meta-analysis showed that LB was associated with decreased costs. The cost decrease could be due to faster discharge, fewer additional analgesic requirements, and decreased complications (Singh et al., 2017).

Limitations

Limitations of this study include the fact that there was no statistical significance for ROM, total opioid consumption, or POD 1 pain scores. Another limitation is that the subgroups did not differentiate the local anesthetic group from the liposomal bupivacaine group. There was high heterogeneity when individual comparisons were done. Meta-regression and sensitivity analysis helped find the causes of heterogeneity. When this article was published an injection technique for Exparel was not yet established. The authors of this article recommend standardization of infiltration techniques, due to high heterogeneity (Singh et al., 2017).

The use of bupivacaine versus LB in abdominal surgeries

Hutchins et al. (2019)

Hutchins et al. (2019) conducted a Level II prospective, randomized, blinded study examining the use of LB versus bupivacaine for transversus abdominis plane (TAP) blocks following robotic and laparoscopic hysterectomies. Patients in the experimental group ($n = 31$) received a bilateral TAP block consisting of 10 mL of 0.25% bupivacaine with 1:200,000 epinephrine and 1.3% LB (10 mL) and normal saline (10 mL) on each side. Patients in the control group ($n = 31$) received sham TAP blocks using 30 mL of normal saline on each side preoperatively, followed by injections at each port site of 0.25% bupivacaine (10 mL) with

1:200,000 epinephrine before extubation. The primary outcome of this study was the total morphine equivalents within 72 hours of surgery. Secondary outcomes included: assessment of postoperative pain at 24,48, and 72 hours postop, PONV, length of recovery time, and complication rates.

Results

Average morphine equivalents were lower in the experimental group over the course of 72 hours following surgery (20.8 mg versus 25 mg), ($p = .03$). In both groups, narcotic use was highest within 24 hours of surgery. There was less difference in narcotic requirements between both groups on POD 2 and 3. Five patients in the experimental group (16.1%) were opioid-free at 72 hours postop, compared to zero patients in the control group. Overall, the patients in the experimental group had decreased total maximal pain scores throughout days 1 through 3 ($p = .022$). Patient satisfaction, length of PACU or hospital stay, and PONV were similar between groups (Hutchins et al., 2019).

Limitations

Specific strategies, such as the number of port sites, were not standardized. The infiltration technique was detailed in the protocol, however compliance was not measured. Another limitation that could have potentially impacted outcomes was that the control group received 100 to 125 mg of bupivacaine whereas, the experimental group received 50 mg of bupivacaine and 266 mg of LB. The saline injection during the sham TAP procedure could have inadvertently caused pain. Lastly, this study relied on patients reporting their pain, due to the fact most were treated as outpatients. The authors suggest that future studies blind the reporter and the observer (Hutchins et al., 2019).

Hutchins, Kesha, Blanco, Dunn, and Hochhalter (2016)

A prospective, randomized, observer-blinded study was performed by Hutchins et al., (2016) that compared TAP blocks using liposomal bupivacaine and TAP blocks using non-liposomal bupivacaine in patients undergoing donor nephrectomies. Patients were randomized to receive TAP blocks using 1.3% liposomal bupivacaine and normal saline ($n = 30$) or 0.25% bupivacaine with adrenaline ($n = 29$).

Results

There were no differences in maximal postoperative pain scores between 0 to 24 hours or 24 to 48 hours. Maximal pain scores in the LB group were 5 versus the non-LB group (6) at 24-48 hours postop ($p = .009$). At 48-72 hours postop, maximal pain scores in the LB group was 3 versus the non-LB group (5) ($p = .02$). Opioid use, measured in fentanyl equivalents, were lower in the LB group (105 mcg) versus 182 mcg in the non-LB group ($p = .03$). Seven patients in the LB group experienced PONV within 72 hours, compared to fifteen patients in the non-LB group ($p = .03$). The average length of stay (in hours) was 67.7 in the LB group compared to 78.1 in the non-LB group ($p = .02$). LB was associated with better pain control, less PONV, and decreased LOS (Hutchins et al., 2016).

Limitations

The anesthetist in charge of performing the TAP block was not blinded. Postoperative analgesic administration of ketorolac and opioids were administered as needed rather than scheduled. Another limitation was that patient satisfaction was not measured. The authors recommend that more randomized multicenter trials be completed in the future to confirm the results of this study. Future studies should also compare LB to other long-acting local anesthetics that are currently being developed (Hutchins et al., 2016).

Barron et al. (2017)

A single-center, double RCT was conducted by Barron et al. (2017) involving fifty-nine patients who underwent laparoscopic hysterectomies. The objective of this study was to determine whether or not a pre-incision injection of LB (266 mg) provided better pain relief than 0.25% bupivacaine (50 mg) following surgery. Each group consisted of thirty-two patients. The primary outcome was overall average pain scores via telephone survey on POD 3. Secondary outcomes included overall average and worst pain scores on POD 1, 2 and 14, in-hospital pain scores, and total narcotic usage.

Results

The LB group had decreased average pain scores on POD 3 ($p = .02$). The LB group also reported lower worst pain scores on POD 2 ($p = .03$) and POD 3 ($p = .01$). No differences existed for opioid use, length of stay, adverse effects, in-hospital pain scores, or pain scores on POD 1 or POD 14. The authors do not support the routine use of LB for port site analgesia in laparoscopic or robotic hysterectomies (Barron et al., 2017).

Limitations

The authors of this study did not list any limitations.

Stokes et al. (2017)

Stokes et al. (2017) conducted a retrospective cohort study to examine the effects of LB for TAP blocks on postoperative pain and opioid consumption following colorectal surgery. The non-LB group received 0.25% bupivacaine (20 mL) on both sides of the incision ($n = 104$). The LB group received 10 mL of LB and 10 mL of saline (20 mL) on both sides of the incision ($n = 303$).

Results

Average pain scores at all times up to 24 to 36 hours were lower in the LB group compared to the non-LB group (4.8 versus 5.5) ($p = .031$). Between 36 to 48 hours postop both groups had similar pain scores ($p = .120$). Patients in the LB group required fewer intravenous opioids (64.5 versus 99), ($p = .04$). Oral opioid requirements were not significantly different between both groups, ($p = .449$). Acetaminophen use was similar between both groups ($p = .219$). Patients in the LB group required less ketorolac (99.1 versus 145.7 mg), ($p = .006$). LOS and cost were not significantly different between both groups. LOS in the non-LB group (5.6 d versus 6.3 d), ($p = .274$). The cost of the LB group totaled \$24,553.46 versus \$21,912.52 in the non-LB group, ($p = .560$) (Stokes et al., 2017).

Limitations

This study was retrospective and had a single-center design. There was also heterogeneity in the administration of blocks. The authors recommend additional studies be completed to examine the cost-effectiveness of LB (Stokes et al., 2017).

Guerra et al. (2019)

Guerra et al. (2019) conducted a Level III retrospective, comparative study involving 100 patients undergoing elective laparoscopic colectomies. Fifty patients received liposomal bupivacaine via TAP blocks (study group). The study group was compared to a retrospective group of fifty patients who received bupivacaine via the TAP block (control group). Outcomes included narcotic requirements during hospitalization, number of days until ambulation, number of days until bowel function, and total hospital LOS. The patients in the control group received 0.25% bupivacaine (80 mL). The patients in the study group received liposomal bupivacaine (20 mL), plain bupivacaine (40 mL), and sterile saline (20 mL).

Results

The study group required fewer narcotics (5.06 versus 18.75 mg), ($p = .0002$). Sixteen patients (32%) in the study group did not require any narcotics postoperatively during their hospital stay, compared to four patients (8%) in the control group, ($p = .005$). The study group had an earlier return of bowel function (1.7 versus 2.4 days), ($p = .0002$). The study group had shorter LOS (2.7 versus 5.4 days), ($p = .0146$). Time to ambulate was shorter in the study group (0.9 versus 1.3 days), although insignificant, ($p = .0521$).

Limitations

Several limitations exist in this study. The surgeons were not blinded. The sample size was somewhat small. Data was collected from two different groups of patients who were assessed at different times. The authors recommend a larger sample size with more focus on cost analysis.

Robertson et al. (2019)

Robertson et al. (2019) conducted a retrospective chart analysis. Patients either received TAP blocks preoperatively and rescue opioids (TAP group) or PCA only (PCA group). The purpose of this study was to compare TAP blocks using LB before laparoscopic sleeve gastrectomy (LSG) and laparoscopic gastric bypass (LRYGB). The primary outcome was narcotic requirements (morphine equivalents).

Results

The TAP group required significantly less opioids ($p = < 0.0001$). The average length of stay was 2 days in the PCA group, compared to 1 day in the TAP group ($p = < 0.0001$). Pain scores during the immediate postoperative period and 12 hours postop were significantly higher in the TAP LRYGB group compared to the PCA LRYGB group ($p = < 0.05$). Pain scores were

significantly higher immediately after surgery in the PCA LSG group versus the PCA LSG group ($p = .0109$) (Robertson et al., 2019).

Limitations

This study is retrospective and not randomized. The TAP group received intravenous narcotics as needed and the PCA group did not. This could have affected narcotic consumption. The authors recommend that future research adheres to strict pain assessment methods (Robertson et al., 2019).

Discussion

Fifteen articles were included in this paper that compare the outcomes of Exparel versus bupivacaine. Of these fifteen articles, twelve focused on the use of liposomal bupivacaine in periarticular injections versus traditional periarticular injections. Two of these articles supported the use of Exparel over bupivacaine. One article credited Exparel for lowering pain scores, decreasing total opioid consumption, extending time to first postoperative narcotic rescue, and allowing for more opioid-free patients upon discharge. Another article credited Exparel for decreasing LOS and providing greater pain relief on POD 1. Eight articles did not recommend the use of Exparel over bupivacaine. Some reasons Exparel was not recommended include no differences in LOS, patient satisfaction, PONV, or other complications. Several studies stated that the results did not justify the high cost. Bagsby et al., (2014) suggested that Exparel might be associated with increased pain from 24 hours postop throughout the hospital stay. Two studies listed findings that supported and rejected the use of Exparel. These studies did not directly state whether the use of Exparel in TKA surgeries was warranted.

Two articles compared the use of Exparel injections versus FNBs. Both of these articles supported the use of Exparel. The results of these studies showed that periarticular injections of

Exparel resulted in decreased opioid usage, better ambulation, decreased falls, faster ambulation, decreased LOS, and ultimately decreased costs.

Six studies examining the outcomes associated with LB TAP blocks in various abdominal surgeries were included in this literature review. Five of the six studies compared LB to bupivacaine. One study compared TAP blocks using LB to patient-controlled analgesia (PCA). Five studies supported the use of LB due to its positive outcomes including improved pain control, decreased PONV, decreased LOS, decreased opioid requirements, quicker return of bowel function, and decreased time to ambulation without an identifiable cost increase. The use of LB was associated with more opioid-free patients at 72 hours postop (Stokes et al., 2017).

Barron et al. (2017) did not support the routine use of LB for port-site analgesia in laparoscopic or robotic surgeries. This study found that LB was associated with decreased average pain on POD 3 however, it did not find any differences in opioid consumption or quality of life.

It is difficult to determine the efficacy of LB since pain is highly subjective among individuals. The studies discussed throughout this manuscript are highly variable, making it difficult to compare results. Many studies use an assortment of pain medications as adjuncts throughout the postoperative period to treat breakthrough pain.

Various techniques for PAIs are used, which could potentially alter the outcomes. There is also a lack of consistency regarding supplemental medications added to the PAIs. Adjuncts include ropivacaine, epinephrine, ketorolac, and clonidine. The timing of medication administration is highly variable. In some of the TKA studies, LB is not injected until after the site is closed. This means it is not injected into the posterior capsule or periosteum. Some articles compare LB outcomes in patients who received spinal anesthesia versus general anesthesia but

do not seem to take into account the differences in outcomes that may be associated with the type of anesthesia used.

Alijanipour et al. (2017) assessed pain at the same times each day, in all patients, regardless of the time of surgery, physical therapy, or administration of pain medications. This could result in a misinterpretation of outcomes. Many studies state that the surgeons were not blinded when injecting the local anesthetics. Data for use of LB in TAP blocks is variable because several different types of abdominal surgeries were examined, including laparoscopic and robotic hysterectomy, laparoscopic sleeve gastrectomy, laparoscopic gastric bypass, donor nephrectomy, and other colorectal surgeries. More studies should be conducted to examine the use of LB on each of these abdominal surgeries to better understand the associated outcomes. All of these factors have the potential to alter the results.

In many studies, Exparel was shown to be more efficacious in TKA by allowing for better ambulation, decreased falls, and faster ambulation compared to FNB. Many studies did not support the use of Exparel while comparing cost versus benefit.

Conclusion

These articles have listed several recommendations for future studies. Some of these recommendations include larger sample sizes, standardized injection techniques, protocols for managing breakthrough pain, and longer follow-up periods. Other ways to improve future studies include determining a standard number of port sites for laparoscopic surgeries, determining a standardized protocol whether postoperative analgesics will be administered as needed or on a scheduled basis, and administering the same drugs and doses of supplemental analgesics to the control and study groups.

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