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Exparel for Postoperative Pain Management: a Comprehensive Review

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Abstract

Purpose of Review Multimodal pain management is the most effective way to treat postsurgical pain. However, the use of opioids for acute pain management has unfortunately been a significant contributor to the current opioid epidemic. The use of opioids should be limited and only considered a "rescue" pain medication after other modalities of pain management have been utilized.

Recent Findings It may be difficult to curtail the use of opioids in the treatment of chronic pain; however, in the postsurgical setting, there is compelling evidence that an opioid-centric analgesic approach is not necessary for good patient outcomes and healthcare cost benefits. Opioid-related adverse effects are the leading cause of preventable harm in the hospital setting. After the realization in recent years of the many harmful effects of opioids, alternative regimens including the use of multimodal analgesia have become a standard practice in acute pain management. Exparel, a long-lasting liposomal bupivacaine local anesthetic agent, has many significant benefits in the management of postoperative pain.

Summary Overall, the literature suggests that Exparel may be a significant component for postoperative multimodal pain control owing to its efficacy and long duration of action.

Keywords Exparel · Postoperative pain · Pain management · Opioid-free · Non-opioid

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Introduction

In the USA, over 70 million surgeries are performed annually. Approximately 20–80% patients experience moderate-to-severe pain during their postoperative course [1]. Postoperative pain is mostly nociceptive in nature, with underlying etiologies including thermal-, mechanical-, or chemical-induced tissue damage [2]. Sociologic factors such as poor initial pain assessment, inadequate clinical knowledge by healthcare provider, or the patient's misconception or poorly conveyed expectations can contribute to it. Timely management of acute postoperative pain not only is vital to patient's surgical experience but also saves valuable healthcare resources by decreasing the length of hospital stay, time to discharge, readmission rates, and time before ambulation [3–5]. Although the incidence is low, mismanagement of acute postoperative pain can lead to chronic pain in up to 50% of patients, which has significant personal, social, and economic implications. Pain has many components including physical, psychiatric, and emotional challenges. Successful postoperative pain management warrants a multidisciplinary approach involving both anesthesiologists and surgeons with a balanced use of pharmacologic and regional anesthetic techniques that target several nociceptive receptors and pathways.

Over the past decade, there has been a tremendous focus on understanding the pathophysiology of pain. Though opioids remain the leading modality to manage postoperative pain, the recent opioid epidemic has motivated clinicians to pursue other multimodal pathways for pain management to mitigate the use of large doses of opioids. These pathways target other receptors than the opioid receptors in the spinal cord to mitigate pain. These include local tissue action by inhibiting prostaglandin, bradykinin, and substance P via COX-2 inhibitors, blocking nerve synapses at peripheral nerve sites with local anesthetics, and targeting other receptors than the opioid in the central nervous system including gabapentinoids, alpha agonists, NMDA antagonists, NSAIDS, and acetaminophen. Drugs such as cyclooxygenase (COX) inhibitors (acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), GABA analogs (gabapentin, pregabalin), $\alpha 2$ agonists (clonidine, dexmedetomidine), *N*-methyl-D-aspartate (NMDA) antagonists (ketamine), local anesthetics (lidocaine, bupivacaine, ropivacaine)) are part of most ERAS (enhanced recovery after surgery) protocols devised by various healthcare institutions to improve clinical outcomes after surgery [••6, 7, 8]. Local anesthetics whether locally infiltrated or used in regional anesthesia techniques have a short half-life when used alone as a single shot. Local anesthetics can be used in continuous nerve catheters using patient-controlled analgesia pumps or combined with additives such as epinephrine, dexamethasone, or clonidine for extended postsurgical pain management, but these are not without limitations. Since repeated administration or using a higher dose of local anesthetics like bupivacaine places patients at increased risk of systemic complications, the search for extended release counterparts continues. Neosaxitoxin, HTX-011, POSIMIR® (sucrose acetate isobutyrate extended-release bupivacaine), and Exparel® (bupivacaine liposome injectable suspension) are some examples of new local anesthetic formulations designed to provide sustained pain relief after surgery [••9].

First described in the 1950s, liposomal drug technology is an important advancement in drug delivery allowing for safe and efficacious delivery of drug particles to patients. Liposomal bupivacaine (Exparel) uses DeFoam technology, releasing drug over an extended period of time. In 2011 the FDA approved Exparel for administration into surgical sites to produce postsurgical analgesia [10]. Since its approval, more clinical trials are being conducted to elucidate the treatment potential of Exparel.

This manuscript discusses postoperative pain, the importance of postoperative pain management, different ways to achieve pain control including multimodal analgesia, what constitutes multimodal analgesia and the rationale behind it, and advantages of multimodal over conventional monotherapy. Furthermore, we discuss the advent of Exparel as a potential solution for better postoperative pain management, pharmacology, clinical efficacy, and drug safety.

Role of Exparel in Postoperative Pain Management

Currently, Exparel® (Pacira Pharmaceuticals, Parsippany, NJ, USA) is the only extended release local anesthetic approved by the FDA for use as a single infiltration at surgical site or with certain nerve blocks. It uses multivesicular liposome (DepoFoam) technology that releases its contents, bupivacaine hydrochloride in a more consistent manner and over an extended period (72–96 h) [••9]. This system enhances pharmacokinetics and pharmacodynamics while reducing risk of toxicity. Several studies including some randomized clinical trials have shown Exparel® to be superior to other modalities [••9]. Although it is primarily approved for postsurgical local analgesia, bunionectomy, hemorrhoidectomy, and interscalene nerve block, it has been successfully used off-label for laparoscopic hysterectomy, femoral nerve block, intercostal nerve block, fascial nerve blocks, epidural injections, and knee, shoulder, and hip arthroplasties [••9, 10, 11••12]. Cost can be a limiting factor for various smaller healthcare facilities to include Exparel® as standard bupivacaine is significantly economical in comparison. Further research is warranted to explore the role of liposomal bupivacaine as an adjunct to multimodal analgesia as it has a potential to replace conventional continuous nerve blocks.

Formulations and Administration Information

Exparel currently comes in two formulations, a 266-mg/20-ml single dose vial or a 133-mg/10-ml single dose vial, both aqueous-milky in appearance. The drug can be reconstituted with preservative-free normal saline or lactated ringers and used within 4 h of reconstitution and should never be reconstituted with water or hypotonic agents as it can result in disruption of the liposomal core. Liposomal bupivacaine should not be administered if the vial has been frozen, if it has been exposed for temperatures greater than 40 °C, or if discoloration is noticed within the vial. This can also disrupt the liposomal core.

Pharmacologic Properties

Liposomal bupivacaine is an amide local anesthetic within a multilamellar liposome made of triglycerides, cholesterol, and phospholipids. The mechanism of action involves the drug binding to voltage-gated sodium channels in nerves. The drug is released by systemic absorption of plain bupivacaine from the liposomal bupivacaine solution, followed by a gradual sustained release from the multilamellar vesicles. Liposomal bupivacaine concentration levels are dependent on the amount injected; the greater the dose injected, the higher the plasma levels. Related to its long half-life, the peak plasma concentration then occurs up to 96-h post injection. It is metabolized by the liver by glucuronide conjugation and dealkylation, and it is then excreted by the kidney. As such, it is recommended that care must be taken in administration of these drugs in patients with severe liver or kidney disease. Liposomal bupivacaine can be administered via infiltration up to a maximum dose of 266 mg and for brachial plexus blocks, up to a maximum of 133 mg.

Side effects of liposomal bupivacaine associated with infiltration administration include nausea, vomiting, and constipation. Side effects associated with a liposomal bupivacaine nerve block include nausea, constipation, and pyrexia. Liposomal bupivacaine does not cross the blood–brain barrier, thus reducing the risk of central nervous system toxicity.

Limitations

Liposomal bupivacaine should not be administered to pregnant women, patients under the age of 18 years, and patients with a history of allergic reaction to liposomal bupivacaine. In animal studies this drug has an increased risk of fetal death. Furthermore, this drug should not be administered for continuous intraarticular infusions due to risk of chondrolysis of the joints involved. It is also not indicated for epidural, intrathecal, intravascular, intraarticular, or regional nerve blocks apart from TAP and ISB blocks [13].

Clinical Efficacy of Exparel

Overall, the literature suggests that Exparel has a clear clinical efficacy in postoperative analgesia as a stand-alone medication [••12, •14, 15, •16, •17, •18, 19–31]. However, certain smaller studies suggest that Exparel could be an important portion of a postoperative multimodal pain control regiment (see Tables 1 and 2).

Table 1 Summary of Research Findings

Article Authors and Year	Surgical Site / Block Site	LB Efficacy compared to control?	Technique in Study Group	Technique in Control Group	Primary Outcome
Hamilton et al. (2016), Cochrane Review	Abdomen, Penile proprothesis, bunionectomy	Lack of Efficacy compared to placebo	TAP, Penile PNB, Ankle PNB	Placebo PAI	N/A
Sun et al. (2018), SR & MA	Shoulder Arthroplasty	Similar Efficacy	LB PAI	INB w/ SLA	VASPS, OC, LOS
Liu et al. (2019), MA	TKA	Similar Efficacy for VASPS, LB Efficacy for ↓OC and ↓PONV	LB PAI	TPAI	VASPS OC PONV
Zhao et al. (2019), SR & MA	TKA & THA	Modest LB Efficacy	LB PAI	Placebo PAI	VASPS OC
Kolade et al. (2019), SR & MA	Shoulder Surgery	Similar Efficacy	LB INB or PAI	INB with SLA	VASPS, OC, AE
Yayac et al. (2019), SR & MA	TKA	LB has modest Efficacy compared to PAI but not PNB	LB PAI	TPAI, SLA PAI, PNB's	VASPS, OC

SR, systematic review; *MA*, meta-analysis; *LB*, Liposomal bupivacaine (Exparel); *TAP* transversus Abdominus Plane block; *PAI* Peri-articular Injection; *INB*, Interscalene Nerve Block; *SLA* Standard Local Anesthetic; *LOS*, hospital Length of Stay; *PONV*, post-operative nausea & vomiting; *VASPS*, Visual Analog Pain Score; *OC*, opioid consumption; *TPAI*, Traditional Peri-Articular Injection; *TKA*, Total Knee Arthroplasty; *THA*, Total Hip Arthroplasty; *AE*, adverse effects (ex: delay to patient mobilization, *PONV*, dizziness)

Table 2 Summary of Research Findings

Article Authors & Year, Study Type	Surgical Site / Block Site	LB Efficacy compared to control?	Technique in Study Group	Block Solution & Block Volume Used	Technique in Control Group	Primary Outcome
Mazloomdost et al. (2017), RCT	Laparoscopic assisted retropubic sling placement	LB Efficacious Compared to Placebo	LB FB	20 ml 1.3% LB + 10 ml NS 30 ml BS	Placebo FB (30 ml NS)	VASPS, OC
Davidovitch et al. (2017), RCT	Ankle Surgery	LB Efficacious Compared to Placebo	LB w/ SLA FB	20 ml 1.3% LB + 20 ml NS 40 ml BS	Placebo FB (40 ml NS)	VASPS, OC
Namdari et al. (2018), RCT	Shoulder Arthoplasty	No Efficacy in LB PAI + LB FB	INB & LB PAI + FB	INB: 15 ml SLA - 20 ml 1.3% LB + 20 mL NS 40 mL LB BS	INB (15 ml SLA)	VASPS, OC
Zlotnicki et al. (2018), RCT	TKA	Minimal Efficacy LB compared to SLA, but both efficacy compared to control	LB FB vs SLA FB	LB FB: 20 ml 1.3% LB 70 ml NS 90 ml BS ---------- SLA FB: 20 ml SLA + 70 mL NS 90 mL BS	No FB	VASPS ROM
Brown et al. (2018), RCT	Lumbar Spine Surgery	No Efficacy compared to placebo	LB FB	20 ml 1.3% LB + 40 ml NS 60 ml BS	Placebo FB (60 ml NS)	VASPS, OC, LOS
Jones et al. (2018), RCT	Posterior Vaginal Wall Surgery	No Efficacy compared to placebo	LB FB	20 lm 1.3% LB 20 ml BS	Placebo FB (20 ml NS)	VASPS, OC
Hernandez et al. (2018), RCT	Hepatectomy	LB TAP Block has efficacy	LB TAP	20 ml 1.3% LB + 30 ml 0.25% SLA + 50 ml NS 100 ml BS	Standard multimodal regiment	VASPS, OC
Lee et al. (2019), RCT	CABG via sternotomy	Minimal efficacy compared to placebo	LB intercos-tal blocks	20 ml 1.3% LB + 30 ml NS 50 ml BS	Placebo blocks (50 ml NS)	VASPS, OC
Hyland et al. (2019), RCT	TKA	No Efficacy compared to standard treatment	LB PAI + A-CB	20 ml 1.3% LB + 40 ml NS 60 ml BS	TPAI + ACB	VASPS, OC, LOS
Colibaseanu et al. (2019), RCT	Elective Bowel Surgery	LB had less efficacy than Pre-operative Intrathecal hydromorphone	LB TAP	20 ml 1.3% LB + 20 ml NS 40 ml BS	Pre-operative Intrathecal Dilaudid	VASPS, OC
Dysart et al. (2019), RCT	TKA	LB-SLA combination had Increased Efficacy Compared to Control	LB-SLA FB	20 ml 1.3% LB 20 ml 0.5% SLA + 80 ml NS 120 ml BS	20 ml 0.5% SLA + 100 ml NS 120 ml BS	OC, LOS, pain satisfac-tion

SR, systematic review; *MA*, meta-analysis; Randomized Controlled Trial; *LB*, Liposomal bupivacaine (Exparel); *TAP*, Transversus Abdominus Plane Block; *PAI* Peri-articular Injection; *INB*, Interscalene Nerve Block; *SLA* Standard Local Anesthetic; *LOS*, hospital Length of Stay; *PONV*, post-operative nausea & vomiting; *VAS*, Visual Analog pain Score; *OC*, opioid consumption; *TPAI*, Traditional Peri-Articular Injection; *TKA*, Total Knee Arthroplasty; *THA*, Total Hip Arthroplasty; *AE*, adverse effects (ex: delay to patient mobilization, PONV, dizziness); *FB*, Field Block; *ROM*, range of motion of surgery joint; *NS*, Normal Saline; *BS*, Block Solution (volume)

Table 1 summarizes a Cochrane review article and five meta-analyses. The Cochrane review article focuses on the potential efficacy of Exparel in 3 different surgical techniques—TAP in abdominal surgery, dorsal penile blocks for penile prosthesis procedures, and ankle blocks for ankle open-reduction-and-internal fixation procedures [23]. The 5 meta-analyses focus on the potential efficacy of Exparel for orthopedic procedures—especially joint procedures [12, •16, •17, •18, 19]. No matter which studies were included in the analyses, visual-analog-score pain scale and postoperative opioid consumption were primary outcomes in all of the studies investigated. The overwhelming conclusion of all of these articles is that no matter what infiltration technique the Exparel solution was used with, it did not have significant efficacy compared with placebo or compared with standard peri-articular infiltration solutions. Two of the articles—Zhao et al. and Yayac et al.—did find modest (but not clinically significant) Exparel efficacy. Another common conclusion drawn by all 6 of these articles was that the studies

included in their analyses lack uniformity—therefore limiting the decisiveness of their conclusions. All of the articles recommend that larger and more standardized studies are needed before a fair determination can be made about the overall efficacy of Exparel.

Table 2 is a chart summarizing the results of 11 randomized control trials published in the past 3 years [14, 20, 25–32]. Since the lack of study uniformity was a major factor in the conclusions of all of the 6 articles discussed previously, the surgery type, type of analgesic block, and Exparel block solution and control group block solution have been described. As one can easily see, there is huge variability in all of these study characteristics. This more than anything shows how diversely clinical researchers are using Exparel to determine its true efficacy. While this diversity is potentially beneficial, it means that it is difficult to draw in the short term. The efficacy conclusions of articles in Table 2 are very wide ranging. Five articles concluded that Exparel solutions are efficacious for the treatment of postoperative pain, 5 articles concluded that Exparel solutions has similar efficacy compared with placebo or standard infiltration solutions, and 1 article concluded that a Exparel TAP solution was less efficacious than the other study modality (one-shot intrathecal hydromorphone) [31].

The true efficacy of Exparel-based block solutions has yet to be determined. Any clinician wishing to incorporate Exparel into their postoperative analgesia regiment should start by thoroughly reviewing the literature to find an Exparel block technique and/or infiltration similar to the one they wish to use in their patient population. If the clinician decides to proceed with using Exparel, they should proceed conservatively and critically think about how to monitor the patient outcomes. Any clinician should also attempt to improve the quality of postoperative pain management for their patient population, but when in doubt, make sure to do no harm.

Safety of Exparel

Exparel has the potential to produce many adverse effects. An association between high plasma concentrations of bupivacaine and cardiovascular and neurologic toxicity is well documented [33]. Adverse events associated with bupivacaine include arrhythmias, cardiac arrest, respiratory arrest, and seizures. Controlled (phases I–III) studies involving 575 patients who received ankle, femoral, and intercostal nerve blocks concluded that liposomal bupivacaine has a similar safety and side effect profile to bupivacaine HCl and saline [34]. The most common adverse reactions to liposomal bupivacaine in clinical trials were nausea, vomiting, constipation, and pyrexia [35, 36] (see Table 3).

All local anesthetics may cause neurotoxicity and myotoxicity at high concentrations, and some controlled release formulations of local anesthetics have also been associated with myotoxicity in animals, even at low concentrations. However, data from preclinical studies in rabbits and dogs did not show toxicity after a single injection of liposomal bupivacaine close to the brachial plexus nerve bundle [37]. The studies concluded that there were no adverse local reactions, even when injected at high concentrations (25 mg/ml) and high dose (30 mg/kg). In a rat study comparing liposomal bupivacaine 25 mg/kg (1.33%) with bupivacaine HCl 10 mg/kg (0.5%) or 25 mg/kg (1.31%) for sciatic nerve block, the frequency of myotoxicity did not differ among the groups, and no neurotoxicity was detected in any group [38, 39].

The safety of infiltration into the surgical site was documented by several randomized, multicenter, double-blind, active-controlled, and placebo-controlled phase II and III trials using surgical models such as inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation, and corrective osteotomy for hallux valgus repair [35, 40–42]. According to the investigators, the drug exhibited minimal adverse events. Bergese et al. compared the cardiac safety of liposomal bupivacaine in four doses (150, 300, 450, or 600 mg) to bupivacaine HCl with epinephrine injected via wound infiltration [41]. They found no significant differences in change from baseline in QRS or QTc duration in the two groups nor did the two groups differ in mean change from baseline heart rate and PR interval. Naseem et al. examined the effect of four doses of liposomal bupivacaine (300, 450, 600, and 750 mg) injected subcutaneously on the QTc interval in healthy volunteers [43]. None of the participants receiving MVL bupivacaine had a maximum QTc interval greater than 500 ms, and there were no changes in QTc of greater than 60 ms at any measured time point.

Liposomal bupivacaine has been studied for epidural and nerve block analgesia in humans. Thirty human volunteers received liposome bupivacaine 89, 155, or 266 mg or bupivacaine HCl 50 mg in the epidural space [44]. It was well tolerated, and the most common adverse event in all treatment groups was injection site pain, which resolved within 30 days for most subjects. In total knee arthroplasty study, patients received a femoral nerve block (FNB) with liposome bupivacaine (67, 133, or 266 mg) or placebo [45]. FNB with liposomal bupivacaine (266 mg) resulted in reduced opioid requirements after surgery with an adverse event profile similar to that of placebo. In lung resection cases, Rice et al. used liposomal bupivacaine to the posterior intercostal nerve blockade and retrospectively compared them with a group of patients who had thoracic epidural analgesia (TEA). There were no significant differences in perioperative complications, in postoperative pain scores, or in narcotic utilization between the liposomal bupivacaine group and TEA group. Additionally, no acute toxicity related to liposomal bupivacaine was observed [46].

The FDA -approved liposomal bupivacaine for interscalene blocks for shoulder surgeries in April 2018. Patel et al. conducted a multicenter, randomized, double-blind controlled trial of 155

Table 3 Adverse reactions of exparel

Incidence greater than or equal to 10%:	Incidence greater than or equal to 2% to less than 10%:	Incidence less than 2%:
Nausea	Pyrexia	Chills
Constipation	Dizziness	Erythema
Vomiting	Peripheral edema	Bradcardia
	Anemia	Anxiety
	Hypotension	Urinary retention
	Pruritis	Pain
	Tachycardia	Edema
	Headache	Tremor
	Insomnia	Postural dizziness
	Postoperative anemia	Paresthesia
	Muscle spasms	Syncope
	Hemorrhagic anemia	Incision site edema
	Back pain	Procedural hypertension
	Somnolence	procedural hypotension
	Procedural pain	procedural nausea
		muscular weakness
		neck pain
		pruritus generalized
		rash pruritic
		hyperhidrosis
		cold sweat
		urticaria
		bradycardia
		palpitations
		sinus bradycardia
		supraventricular extrasystoles
		ventricular extrasystoles
		ventricular tachycardia
		hypertension
		pallor
		anxiety
		confusional state
		depression
		agitation
		restlessness
		hypoxia
		laryngospasm
		apnea
		respiratory depression
		respiratory failure
		body temperature increased
		blood pressure increased
		blood pressure decreased
		oxygen saturation decreased
		urinary incontinence
		vision blurred
		tinnitus
		drug hypersensitivity
		hypersensitivity

patients demonstrating that the product was safe for interscalene blocks and has similar safety profile to saline placebo group [47]. Clinical trial data is not sufficient, however, to support the general use of liposomal bupivacaine for regional nerve blocks other than shoulder surgery.

There are limited clinical studies analyzing liposomal bupivacaine and local anesthetic systemic toxicity (LAST). Per the FDA, LAST is an associated adverse event for injectable local anesthetics. The toxic dose of liposomal bupivacaine is unknown. The manufacturer states that injection of liposomal bupivacaine must not occur within 20 min after the administration of non-bupivacaine local anesthetics, because it could cause the immediate release of bupivacaine from the liposomes. It may be mixed in the same syringe as bupivacaine HCl or administered immediately after a dose of bupivacaine HCl as long as the bupivacaine dose is ≤ 50% of the liposomal bupivacaine dose. Avoid the use of other local anesthetics within 96 -h following administration of liposomal bupivacaine. It is not recommended to be used in patients < 18 years old and/or pregnant patients. Because amide-type local anesthetics are metabolized by the liver, liposomal bupivacaine should be used cautiously in patients with hepatic disease. Currently, the medication is contraindicated in obstetrical paracervical block anesthesia.

Pediatric Use

While the safety and effectiveness in pediatric patients below the age of 18 have not been established by the FDA, there are completed trials that suggest it may be useful in pediatric patients. Pacira Biosciences has reported positive results from its phase 3 study of Exparel in pediatric patients who underwent spinal or cardiac surgeries. The findings were consistent with pharmacokinetic and safety profiles for adult patients, with no additional safety concerns identified at a dose of 4 mg/kg [48]. Another retrospective case–control study of pediatric patients who underwent pharyngoplasty demonstrated the first safe use of Exparel in pediatric patients with improved pain control following surgery [49]. Furthermore, a retrospective, single-center, assessor-blinded cohort study found that pediatric surgical patients receiving wound infiltration with either plain or liposomal bupivacaine showed no cases of local anesthetic systemic toxicity syndrome [50]. Additionally, while Exparel may be well tolerated in pediatric patients, there is evidence to suggest that it does not reduce opioid consumption after spinal surgery. A 2018 retrospective matched cohort study in pediatric patients who underwent posterior spinal fusion surgery, found that liposomal bupivacaine was not associated with reductions in postoperative opioid use in pediatric spinal surgery [51].

Conclusion

Exparel may be a potential breakthrough treatment for the management of postoperative pain [52]. However, more studies are warranted to demonstrate its use in wide variety of procedures postsurgery and to better assess the utility of liposomal bupivacaine as an integral part of multimodal pain management protocol [52]. Despite causing prolonged analgesia and opioid-sparing effect allowing for accelerated rehab, it can cause nausea, vomiting, pyrexia, dizziness, headache, peripheral edema, hypotension, tachycardia, somnolence, and increase risk of granulomatous inflammation and inhibitory effects of platelet aggregation and QTc prolongation on EKG. It may also cause side effects such as seizures, cardiac toxicity, and cardiac arrest with IV injection or overdose. The gamut of side effects is very similar to plain bupivacaine. As an amide local anesthetic, it is metabolized in the liver and hence needs to be cautiously used in patients with hepatic dysfunction [52, 53]. The appearance should not be confused with propofol as both are milky white. The drug error can lead to toxic effects and death. It is contraindicated in obstetrical paracervical block anesthesia [54].

Current literature has demonstrated Exparel to provide prolonged analgesia and opioid-sparing effect as compared with placebo, however, its cost-effectiveness and increased analgesic efficacy in comparison with plain bupivacaine in various clinical settings with well-powered trials are yet to be studied. Its use in pregnant populations and via perineural, intrathecal, or epidural routes warrants more trials. Its use in pediatric populations seems promising, but more studies are warranted before FDA approval. Presently, it has a limited treatment role as there are no studies to support the conclusion that liposomal bupivacaine yields better outcomes when compared to the stand of care treatment [33].

The drug has shown to decrease the length of hospital stay, but an overall decrease in health costs related to hospitalization is not yet established. In fact, the cost of Exparel over generically available alternatives may be a significant burden on hospitals and healthcare systems. This warrants further studies to show the potential cost implications [10]. Overall, Exparel may still have a role for postoperative pain control in ambulatory and outpatient surgery patients who may experience adverse effects of opioids or in whom NSAIDS are contraindicated. However, more trials are necessary to assess the efficacy and duration of analgesia, different routes of administration, and further FDA-approval for treating other conditions.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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