

Liposomal extended-release bupivacaine for postsurgical analgesia

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Abstract: When physicians consider which analgesia to use postsurgery, the primary goal is to relieve pain with minimal adverse side effects. Bupivacaine, a commonly used analgesic, has been formulated into an aqueous suspension of multivesicular liposomes that provide long-lasting analgesia for up to 72 hours, while avoiding the adverse side effects of opioids. The increased efficacy of liposomal extended-release bupivacaine, compared to bupivacaine hydrochloride, has promoted its usage in a variety of surgeries including hemorrhoidectomy, bunionectomy, inguinal hernia repair, total knee arthroplasty, and augmentation mammoplasty. However, like other bupivacaine formulations, the liposomal extended-release bupivacaine does have some side effects. In this brief review, we provide an update of the current knowledge in the use of bupivacaine for postsurgical analgesia.

Keywords: bupivacaine, liposome, analgesia, side effects, efficacy, patient satisfaction

Introduction

Postoperative pain management and minimal analgesic adverse side effects are critical factors in improving patient satisfaction.^{1,2} The systemic analgesic effects of opioids decrease pain in patients, but opioids are known to cause adverse side effects including nausea, dizziness, vomiting, urinary retention, constipation, pruritus, bradypnea, and sedation.^{3,4} These opioid-related symptoms often lead to a significant increase in total hospital cost and length of stay.⁵ Local analgesics have been utilized to avoid these side effects, but it is now known that they carry side effects of their own including but not limited to: chondrotoxicity, human tendon stem cell cytotoxicity, and intervertebral disk cytotoxicity. Furthermore, local analgesics have a short time of action, usually lasting less than 8 hours in adults.^{6,7} In order to prolong duration of action, catheters are inserted to the target site and connected to a local infusion pump, thereby analgesics are delivered to relieve pain with minimal adverse effects.^{8,9} However, the use of infusion pumps is often associated with tissue necrosis and wound infection.¹⁰ In order to provide long-lasting analgesia through single-dose administration, bupivacaine has been formulated with liposomes to create liposomal extended-release bupivacaine. One example of such a bupivacaine liposome injectable suspension is EXPAREL[®] (Pacira Pharmaceuticals, Inc., San Diego, CA, USA). EXPAREL[®] is an aqueous suspension of multivesicular liposomes (DepoFoam[®] drug delivery system; Pacira Pharmaceuticals, Inc.) containing bupivacaine at a concentration of 13.3 mg/mL. After injection of EXPAREL[®] into soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time. In this review, we will update the clinical use of EXPAREL[®] and related analgesics.

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Bupivacaine liposome injectable suspension

In 2006, Cocoran et al¹¹ conducted a survey of 135 academic anesthesiology departments and found that 55% of them preferred bupivacaine hydrochloride (HCl) as their local anesthetic of choice. Due to its novel design and slow release, EXPAREL[®] can produce local analgesia for up to 72 hours,¹² about ten times longer than bupivacaine HCl.¹³ EXPAREL[®] has greater upfront costs than bupivacaine HCl. The most recent wholesale acquisition cost for a vial of EXPAREL[®] 266 mg/20 mL is \$14.25 (pricing from December 1, 2011) compared to a 10 mL vial of 0.25% bupivacaine HCl costing \$0.291 (pricing from April 1, 2012; of note, the wholesale acquisition cost represents published catalog price and may not be the actual transaction cost price). The overall costs for patients using EXPAREL[®] are likely cheaper than for bupivacaine HCl in patients who need long-term analgesia due to decreased need for opioids.¹⁴ To our knowledge, no study has directly evaluated hospital cost or length of stay between EXPAREL[®] and bupivacaine HCl; however, it has been documented that the mean difference of cost and length of hospital stay between an EXPAREL[®]-based multimodal analgesia regimen (\$8,766 and 2.0 days) and an opioid-based regimen (\$11,850 and 4.9 days) was \$3,084 and 2.9 days in patients undergoing open colectomies.¹⁵

Bupivacaine blocks sodium channels during an action potential, thus inhibiting generation and conduction of nerve impulses initiated by painful stimuli.¹⁶ Chahar and Cummings¹⁷ described in detail the structure, pharmacodynamics, and pharmacokinetics of this new liposomal bupivacaine. The extended-release advantage of EXPAREL[®] has promoted its widespread use in surgical procedures such as hemorrhoidectomy, bunionectomy, inguinal hernia repair, total knee arthroplasty, augmentation mammoplasty, and colectomy.

Patient satisfaction and efficacy

Patients will have little tolerance of a drug that has numerous adverse effects, making this a necessary parameter in comparing drug choice. Baxter et al¹⁸ and Viscusi et al¹⁹ retrospectively reviewed ten randomized, double-blinded studies to determine total adverse events after administration of 66 mg to 532 mg EXPAREL[®] or 75 mg to 200 mg bupivacaine HCl. Adverse events (AEs) were classified as wound complications, wound healing times, and wound scarring. Local AEs, including erythema, drainage, edema, and induration, were noted over 36 days. Baxter et al found that the percent incidence of AEs was similar across both modes of analgesia.¹⁸ AEs occurred in 9%–20% of 823 patients who received EXPAREL[®] compared to 8%–19%

AEs in 446 patients who were treated with bupivacaine HCl. Furthermore, wound-healing and bone-healing at doses up to 532 mg EXPAREL[®] appeared similar to the bupivacaine HCl group. In contrast, Viscusi et al noted 62% of patients had AEs when they received EXPAREL[®], compared to 75% of patients who received bupivacaine HCl and 43% of the patients treated with placebo.¹⁹ Furthermore, serious AEs were noted in 2.7% of EXPAREL[®] users versus 5.4% of bupivacaine HCl users.

Dasta et al²⁰ examined the postsurgical use of EXPAREL[®] at doses \leq 266 mg versus bupivacaine HCl at doses \leq 200 mg. A total of nine double-blinded studies were pooled and analyzed from five surgical procedures including inguinal hernia repair, total knee arthroplasty, breast augmentation, hemorrhoidectomy, and bunionectomy. Patient outcomes were evaluated by cumulative pain intensity scores (area under the curve) based on a numerical rating scale throughout a period of 72 hours after surgery. The cumulative pain intensity score was found to be lower in patients using EXPAREL[®] than in patients using bupivacaine HCl (283 versus 329, $P=0.039$). The median time until opioid rescue was 10 hours when using EXPAREL[®], compared to 3 hours when using bupivacaine HCl. Furthermore, opioid usage was decreased from 19 mg in the bupivacaine HCl group to 12 mg in the EXPAREL[®] group, suggesting a decrease in the opioid-related AEs.

By focusing on a dose of 266 mg EXPAREL[®] post hemorrhoidectomy, Haas et al²¹ found that the median time until opioid rescue was 19 hours, much longer than the 8 hours noted in the patients who received bupivacaine HCl ($P=0.05$). AEs related to opioids were also found in 35% of the patients injected with bupivacaine HCl compared to only 4% of the patients injected with 266 mg EXPAREL[®].

Bramlett et al²² compared the efficacy and safety of 150 mg bupivacaine HCl with 1:200,000 epinephrine versus EXPAREL[®] at doses of 133 mg, 266 mg, 399 mg, and 532 mg, following total knee arthroplasty. The double-blinded study found that the cumulative pain intensity scores through 4 days postsurgery were 20.7, 19.5, 18.8, and 19.1, for using EXPAREL[®] at doses of 133 mg, 266 mg, 399 mg, and 532 mg, respectively, compared to a cumulative pain intensity score of 20.4 when using bupivacaine HCl at a dose of 150 mg. Smoot et al²³ conducted a randomized, double-blinded study on 136 patients who underwent submuscular augmentation mammoplasty and compared the pain and opioid usage after a single 600 mg dose of EXPAREL[®] and a single 200 mg dose of bupivacaine HCl. The mean cumulative pain scores (numerical rating scale with activity through 3 days) were 441.5 using EXPAREL[®] and 468.3

using bupivacaine HCl ($P = 0.3999$). EXPAREL[®] usage was associated with a significant decrease in opioids consumed during the first 24 hours ($P = 0.0211$) and 48 hours ($P = 0.0459$). Bergese et al²⁴ analyzed a pool of 823 patients, from ten randomized, double-blinded studies, who were injected via local wound infiltration sites with EXPAREL[®] (doses varied from 66 mg to 532 mg). Another group of 446 patients were injected with bupivacaine HCl at doses ranging from 75 mg to 200 mg, and 190 patients were included in a placebo group. The pain intensity scores were lower in the EXPAREL[®] group than in the placebo group in 16 of the 19 treatment arms analyzed ($P < 0.05$). In contrast, only five of the 17 treatment arms using bupivacaine HCl had a lower pain score than the placebo group ($P < 0.05$).

The efficacy of EXPAREL[®] was further supported by the mean time until opioid usage, consumption of opioids, and patient/care provider satisfaction with postsurgical analgesia. Golf et al²⁵ compared EXPAREL[®] to placebo in a randomized study of 193 patients who had undergone bunionectomy. Ninety-six patients were placed in the placebo group, while 97 patients were administered 120 mg of EXPAREL[®] through wound infiltration before closure. Over the first 24 hours and 36 hours, EXPAREL[®] significantly decreased pain compared to the placebo ($P = 0.0005$ and $P < 0.0229$, respectively). Patients also avoided opioid usage at a greater rate than placebo when injected with EXPAREL[®] (7.2% versus 1% of patients, $P < 0.0404$). The median time until first opioid usage was prolonged by EXPAREL[®] compared to placebo (7.2 hours versus 4.3 hours, $P < 0.0001$). Gorfine et al²⁶ conducted a double-blinded study with 186 patients, comparing EXPAREL[®] and placebo to assess postsurgical analgesia benefits. Pain intensity scores were lower in patients using EXPAREL[®] than in patients using placebo (141.8 versus 202.5, $P < 0.001$). The mean usage of opioids over the first 72 hours was 22.3 mg and 29.1 mg for EXPAREL[®] and placebo groups, respectively ($P < 0.0006$). The median time until first opioid usage was 14.3 hours and 1.2 hours for the EXPAREL[®] and placebo groups, respectively. Most importantly, 95% of patients in the EXPAREL[®] group were satisfied with their postsurgical analgesia, compared to 73% of patients in the placebo group ($P = 0.0007$). Based on the

forementioned studies, a comparison between EXPAREL[®] and bupivacaine HCl is summarized in Table 1.

Systemic toxicities

It is well documented that bupivacaine HCl can prolong QTc intervals (corrected intervals between the Q wave and T wave) and cause ventricular arrhythmias through potassium channel blockade.^{27–29} Borgeat et al³⁰ also noticed an increase in the PQ interval within 15 minutes of 5 mg/mL injection of bupivacaine. The prolongation continued for 1 hour, when the PQ interval shortened to near normal ranges. Furthermore, they reported no change in QRS, QT, or QTc intervals. However, current research suggests that EXPAREL[®] has a better cardiac safety profile compared to standard bupivacaine injections. Naseem et al³¹ conducted a study in healthy patients, evaluating their QTc intervals at doses of 300 mg, 450 mg, 600 mg, and 750 mg EXPAREL[®]. The alteration of QTc intervals by EXPAREL[®] was compared to changes caused by moxifloxacin. The authors found that moxifloxacin induced QTc prolongation of 12 seconds with a two-sided 95% confidence interval above 10 seconds. EXPAREL[®] at doses of 300 mg, 450 mg, 600 mg, and 750 mg caused the QTc interval to decrease by 2.24, 2.45, 3.6, and 7.67 milliseconds, respectively. Only the 600 mg dose fell short of the significance level of the two-sided 95% confidence interval. This study suggests that EXPAREL[®] reduces QTc intervals and may be a safer, long-lasting alternative to bupivacaine HCl.

Bupivacaine also carries significant risk of toxicity in the central nervous system if given in overdose or injected intravenously. Feldman et al³² found that the mean dosage to cause seizures in dogs after intravenous bupivacaine injection was as low as 8.6 mg/kg, leading to a mean duration of seizure of 307 seconds. Since substantial plasma concentrations of bupivacaine are required to cause toxicities in the central nervous system, it should be of minimal concern if the local anesthetic is properly administered.

Local toxicities

Intervertebral disk cell cytotoxicity, myocyte toxicity, chondrotoxicity, and granulomatous inflammation are potential localized side effects of EXPAREL[®] injection. The most

Table 1 Comparison between EXPAREL[®] and bupivacaine HCl

Formulation	Costs	Pain intensity scores	Time until opioid rescue (h)	% adverse events
EXPAREL [®]	\$14.25/20 mL	283*, 441.5 [†]	10*, 19 [#]	9–20% ^π , 62% ^λ
Bupivacaine HCl	\$0.291/10 mL	329*, 468.3 [†]	3*, 8 [#]	8–19% ^π , 43% ^λ

Notes: *Baxter et al;¹⁸ ^λViscusi et al;¹⁹ ^πDasta et al;²⁰ [#]Haas et al;²¹ [†]Smoot et al.²³

Abbreviation: HCl, hydrochloride.

benign of these side effects is a small amount of granulomatous inflammation due to liposome degradation.^{10,33}

Chondrotoxicity appears to be a much more salient problem in intra-articular usage of EXPAREL[®], like other local anesthetics, which is why Pacira Pharmaceuticals, Inc., does not recommend intra-articular use of EXPAREL[®]. While an intra-articular injection of 0.125% bupivacaine does not induce chondrocyte death, 0.25% bupivacaine is significantly chondrotoxic after 60 minutes exposure.³⁴ Alarming, Chu et al³⁵ reported that an intra-articular injection of 0.5% bupivacaine led to a 50% loss in chondrocyte density with no obvious cartilage loss. Chondrotoxicity has been investigated most extensively in the glenohumeral joint. Wiater et al³⁶ conducted a prospective level II cohort study analyzing 375 cases of arthroscopic shoulder surgeries to assess chondrolysis from intra-articular injections of bupivacaine and lidocaine. Survival analysis was implemented to assess chondrocyte death, and the strength of these results was computed as hazard ratios estimated from the Cox proportional hazard model. Both adjusted and unadjusted Cox proportional hazard models were used to account for the variability due to patient age and the date of surgery. Of the 375 surgeries, 49 patients suffered from chondrolysis, with half being identified within the first 18 months postsurgery. Each patient was known to have postsurgical intra-articular injection of bupivacaine or lidocaine ($P < 0.001$, Cox regression). No chondrolysis was found in patients who did not receive intra-articular injections of local anesthetics. In another study, Anderson et al³⁷ reported 18 individuals diagnosed with glenohumeral chondrolysis, all of them had received intra-articular injections of bupivacaine through an intra-articular pain pump catheter. No thermal energy was used as part of their operation. Decreased range of motion was also noted as a result of the surgeries. These studies caution against intra-articular injection of EXPAREL[®] or other local anesthetics. This precaution is further supported by a study of patients with damaged cartilage.³⁸ A recent in vitro study has shown that hyaluronan can prevent chondrocyte death caused by bupivacaine at supraphysiological temperatures.³⁹ However, whether coinjection of hyaluronan and bupivacaine intra-articularly may alleviate bupivacaine's chondrotoxicity awaits further evidence from in vivo studies.

It should be noted that the use of EXPAREL[®] has not been approved by the US Food and Drug Administration for spinal usage. To the best of our knowledge, no studies have been published in evaluating the use of EXPAREL[®] versus standard bupivacaine as a local anesthetic in spinal procedures. However, bupivacaine HCl is an anesthetic used in spinal procedures, and in vitro studies have shown that it is

toxic in a dose- and time-dependent manner. Doses as small as 0.25% bupivacaine induced nearly 100% cell death in the annulus pulposus and nucleus pulposus cells of intervertebral disks.^{40,41} These results have been supported by the results from an ex vivo mouse model in which bupivacaine reduced both cell viability and synthesis of matrix proteins.⁴² Coinjection of 1 mg triamcinolone with bupivacaine has been shown to have a protective effect on intervertebral disk cells.⁴³

Bupivacaine is also known to cause acute skeletal muscle degeneration with a slow but nearly maximal regeneration after 2 months.⁴⁴ A possible mechanism of myotoxicity is through induction of calcium release from the sarcoplasmic reticulum, while concurrently inhibiting calcium reuptake.⁴⁵ Although the muscle tissue is capable of regeneration after injection of bupivacaine at doses as high as 0.75%, late-stage scarring has been found. This damage is dose-dependent because injection of bupivacaine at doses $<0.38\%$ does not cause any long-term damage.⁴⁶ Although most studies typically focus on adults, myonecrosis may be even more pronounced in children due to oxidative mitochondrial changes.⁴⁷ Furthermore, the toxicity does not appear to be limited only to the muscle fibers. Haasters et al⁴⁸ has reported that 0.5% bupivacaine has cytotoxic effects on human tendon stem cell/progenitor cells, while morphine had no effect on apoptosis or decreased cell survival. Both erythropoietin⁴⁹ and N-acetylcysteine⁵⁰ may confer a protective action against bupivacaine-induced myocyte death.

Discussion

EXPAREL[®] has been found to be a more effective pain management treatment than standard bupivacaine in inguinal hernia repair, bunionectomy, hemorrhoidectomy, and breast augmentation surgery. There is a clear increase in efficacy in using EXPAREL[®] compared to using bupivacaine HCl, and no significant difference in AEs has been reported. Furthermore, EXPAREL[®] is likely to cost patients less money than bupivacaine HCl due to diminished opioids usage and shortened hospital stays. However, caution should be taken when performing the cost-benefit analysis of EXPAREL[®] injection as the main pain management therapy. Both intra-articular and spinal injections should be cautioned due to potential toxic effects and permanent damage to cartilage and intervertebral disk cells. Granulomatous inflammation and myonecrosis have not been found to cause permanent long-term damage at normal EXPAREL[®] dosages. Furthermore, cardiotoxicity does not appear to be significant compared to bupivacaine HCl. We conclude that EXPAREL[®] has potential value to decrease the length of hospital stay and increase patient satisfaction if used properly.

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Disclosure

The authors report no conflicts of interest in this work.

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