A Double-Blind, Randomized, Active-Controlled Study for Post-Hemorrhoidectomy Pain Management with Liposome Bupivacaine, a Novel Local Analgesic Formulation

ERIC HAAS, M.D.,* EROL ONEL, M.D.,† HOWARD MILLER, M.D.,‡ MADHU RAGUPATHI, M.D.,*
PAUL F. WHITE, PH.D., M.D.§

*From the *Colorectal Surgical Associates, Ltd, LLP, Houston, Texas; †Pacira Pharmaceuticals, Inc., Parsippany, New Jersey; ‡The Woman's Hospital of Texas and Fannin Surgicare, Houston, Texas; and the §Cedars-Sinai Medical Center, Los Angeles, California*

This randomized, active-controlled study evaluated the extent and duration of analgesia after administration of liposome bupivacaine (LB), a novel formulation of bupivacaine, compared with bupivacaine HCl given via local infiltration in excisional hemorrhoidectomy. One hundred patients were randomly assigned to receive a single dose of bupivacaine HCl 75 mg (0.25% with 1:200,000 epinephrine) or LB 66, 199, or 266 mg upon completion of hemorrhoidectomy. Postoperative pain intensity was assessed using a numeric rating scale at rest to calculate a cumulative pain score (area under the curve). Cumulative pain scores were significantly lower with LB at each study dose ($P < 0.05$) compared with bupivacaine HCl 72 hours after surgery. *Post hoc* analysis showed that mean total postoperative opioid consumption was statistically significantly lower for the LB 266-mg group compared with the bupivacaine HCl group during the 12- to 72-hour postoperative period ($P = 0.019$). Median time to first opioid use was 19 hours for LB 266 mg *versus* 8 hours for bupivacaine HCl ($P = 0.005$). Incidence of opioid-related adverse events was 4 per cent for LB 266 mg compared with 35 per cent for bupivacaine HCl ($P = 0.007$). Local infiltration with LB resulted in significantly reduced postsurgical pain compared with bupivacaine HCl in patients after hemorrhoidectomy surgery.

OVER 98 MILLION SURGERIES are performed annually in the United States, of which approximately 53 million occur in ambulatory (or short-stay) settings.[1, 2] Despite an increased focus on improving pain management over the last several years, up to 82 per cent of patients continue to experience unacceptable levels of pain after surgery.[3, 4] Inadequate pain control is a major cause of prolonged hospitalization after ambulatory surgery,[5] and many outpatients continue to experience unacceptable postsurgical pain after discharge despite receiving standard analgesic regimens.[3]

Excisional hemorrhoidectomy is associated with significant postsurgical localized pain resulting from surgical incision of the sensitive anal mucosa.[6] This localized model of prolonged pain seems particularly suited for use of an extended-release local anesthetic formulation as part of a multimodal approach to postsurgical pain management.

Address correspondence and reprint requests to Paul F. White, Ph.D., M.D., White Mountain Institute, 144 Ashby Lane, Los Altos, CA 94022. E-mail: paul.white@cshs.org.

Studies have shown that local infiltration with conventional local anesthetics results in effective postsurgical pain management (*i.e.,* lower pain scores and/or reduced consumption of analgesic medication), although the duration of analgesia is generally limited to $\leq$ 8 hours.[7–11] Catheter delivery systems for continuous administration of local anesthetics may be used to extend the duration of analgesia;[12–15] however, the utility of these systems has been limited by the cost of the equipment, the difficulty maintaining the correct position of the catheter, and the resources needed to manage their use in the outpatient setting.[16] Liposome bupivacaine (LB; EXPAREL®, Pacira Pharmaceuticals, Inc., Parsippany, NJ; bupivacaine liposome injectable suspension) is a novel formulation of bupivacaine consisting of microscopic, spherical, multivesicular liposomes (the DepoFoam drug delivery system) composed of numerous nonconcentric internal aqueous chambers containing encapsulated bupivacaine. The structure of the DepoFoam liposomes allows for diffusion of bupivacaine over an extended period after wound infiltration. This delivery system has been used for

over a decade through epidural administration with morphine sulfate extended-release liposome injection (DepoDur®, EKR Therapeutics Inc., Bedminster, NJ) and cytarabine liposome injection for intrathecal administration (DepoCyt® Sigma Tau Pharmaceuticals Inc., Gaithersburg, MD).

We designed this Phase 2 dose-ranging study to assess three dose levels of LB compared with bupivacaine HCl with respect to the extent and duration of analgesia as reflected in pain intensity scores and postsurgical consumption of opioid rescue medication, after single-dose administration via local infiltration in patients undergoing excisional hemorrhoidectomy.

Methods

This double-blind, randomized, active-controlled exploratory study assessed the safety and efficacy of LB through a triple-dose–range, parallel-group comparison with bupivacaine HCl/epinephrine (Marcaine® 0.25% with epinephrine 1:200,000, Hospira, Inc., Lake Forest, IL) administered via local infiltration for postoperative analgesia in posthemorrhoidectomy patients. This multicenter study was conducted between July 2007 and January 2008 at 6 centers in the United States (U.S. clinical trials identifier NCT00529126) and 3 centers in the Republic of Georgia. The study protocol and informed consent were approved by an Institutional Review Board or Independent Ethics Committee at each study center. Written informed consent was obtained from all patients before study enrollment. All study procedures were conducted in accordance with the International Conference on Harmonisation Good Clinical Practices and the Declaration of Helsinki and its amendments.[17]

Study Patient Criteria

Eligible participants included men and nonpregnant women ≥18 years of age with an American Society of Anesthesiologists physical status classification of 1 to 3 scheduled to undergo two- or three-column excisional hemorrhoidectomy (with a cumulative incision length of ≥3 cm) under general anesthesia. Patients were excluded if they weighed less than 50 kg, had clinically significant abnormal laboratory results or a history of clinically significant medical conditions (including cardiovascular, hepatic, renal, neurologic, psychiatric, or metabolic disease; alcohol/substance abuse), or if they had taken a long-acting opioid within 3 days or any opioid within 24 hours before surgery. Patients with a concurrent medical condition or surgery that may have required analgesic treatment for postoperative pain that was not strictly related to the hemorrhoidectomy were also excluded.

Study Design

The parallel-group study design included a screening visit, during which eligibility criteria were assessed, informed consent was obtained, past medical and surgical histories were recorded, vital signs were measured, a pregnancy test was conducted, and self-assessment measurement training was performed. A physical examination was completed and the EQ-5D™ (EuroQol Group, Rotterdam, The Netherlands) quality of life (QOL) questionnaire was administered (higher scores reflected better health status) at the baseline visit. A comprehensive medication history was also obtained for the 3-day period before the day of surgery. Patients were then enrolled in the study in two consecutive cohorts. In Cohort 1, patients were randomized to receive LB 66 mg, LB 199 mg, or bupivacaine HCl 75 mg with epinephrine in a 1:1:1 ratio. An unblinded committee conducted an interim analysis to determine the efficacy of LB 66 mg and 199 mg and an LB 266-mg treatment arm was added for Cohort 2 (Fig. 1). The milligram dose of LB is expressed as the free base (*i.e.,* 266 mg of bupivacaine base is chemically equivalent to 300 mg of bupivacaine HCl).

Induction and maintenance of general anesthesia for the hemorrhoidectomy procedures were not standardized across study sites, but were performed and managed according to the standard of practice at each study

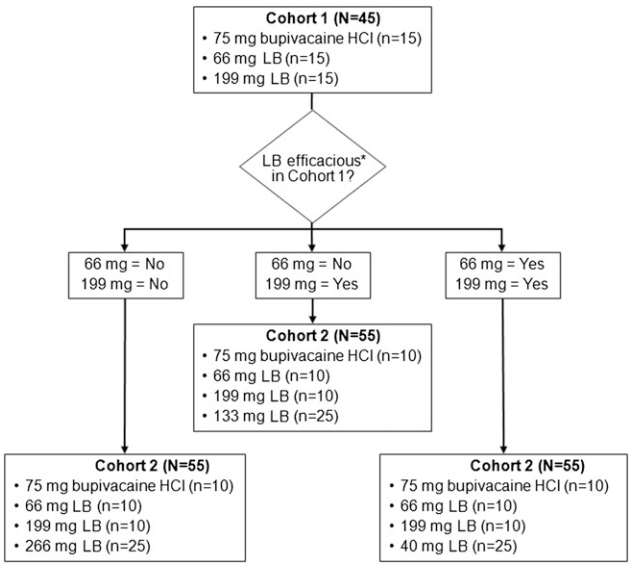

FIG. 1. Dose levels for Cohort 1 and scenarios for Cohort 2. Based on the apparent efficacy of the LB 66-mg and 199-mg dose levels used in Cohort 1, a dose of 40, 133, or 266 mg could have been chosen as the third LB dose level used in Cohort 2. Based on the findings from Cohort 1, LB 266 mg was chosen as the third dose level for Cohort 2. Patients in Cohort 2 were randomized in a 1:1:2.5:1 ratio to receive LB 66, 199, or 266 mg, or bupivacaine HCl 75 mg, respectively. *Efficacious, appears to provide clinically significant prolonged analgesia compared with bupivacaine HCl based on pain scores and opioid consumption.

site. Postbaseline assessments were timed from the start of study drug infiltration (Day 1). All doses of study medication were diluted with preservative-free 0.9 per cent sodium chloride to a final volume of 30 mL for injection at the end of surgery. Study medication was administered in 5-mL increments via infiltrative moving-needle technique in a fan-like fashion to the perianal tissues just outside the external sphincter (Fig. 2). Because LB and bupivacaine HCl are visually distinguishable, study medications were dispensed via sheathed syringes by study personnel not involved with any protocol-specific postsurgical assessments. All staff members involved with study-related evaluations remained blinded throughout the study. At the end of surgery, patients also received a single 30-mg dose of intravenous ketorolac. Patients in the recovery room who needed postoperative analgesia but were unable to tolerate oral medications received parenteral opioids (*e.g.,* intravenous fentanyl 10–25 μg), along with antiemetic medication, as needed. Once patients were able to tolerate oral intake, they received 1000 mg of acetaminophen three times daily during the 96 hours after study drug administration. Postsurgical pain was managed with 5 to 10 mg of oral oxycodone (United States) or 2.5 to 5 mg of parenteral morphine sulfate (Republic of Georgia) every 4 to 6 hours as needed. No other pain medications were permitted during the first 96 hours, unless pain could not be effectively controlled by the protocol-prescribed regimen. Antiemetic medications were given as needed; low-dose aspirin (≤100 mg/day) was allowed for platelet inhibition if needed.

Patients were discharged from the study center in accordance with the local standard of practice. Because the focus of the study was on assessments conducted during the postsurgical period, specific data related to duration of surgery and duration of hospital and recovery room stays were not captured. Vital signs were measured during the first 3 hours after administration of the study drug. Pain intensity was assessed using an 11-point numeric rating scale at rest (NRS, where 0 = no pain and 10 = worst possible pain) at the end of general anesthesia, before the first dose of rescue opioid medication, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96 hours after study medication was administered. Time and date of each bowel movement (BM) and NRS-BM scores were recorded for each BM through 96 hours. All adverse events (AEs) and concomitant medications administered through the first 96 hours were recorded. The EQ-5D™ was administered at 48, 72, and 96 hours after administration of study medication. Patients were instructed to avoid postsurgical constipation by eating a high-fiber diet and drinking plenty of noncaffeinated liquids. Stool softeners and laxatives were prescribed as needed and the surgical site was to be cleaned three times daily and after each BM for the first week after surgery. The use of topical or intrarectal medication was not permitted, unless necessary to treat an AE. Patients returned to the study center on Day 8 for assessment of AEs, vital signs, and the blinded care provider's satisfaction with postsurgical analgesia (0 = completely unsatisfied with patient's analgesia; 10 = completely satisfied with patient's analgesia), and on Day 30 for assessment of AEs, vital signs, and date of return to work or normal activities.

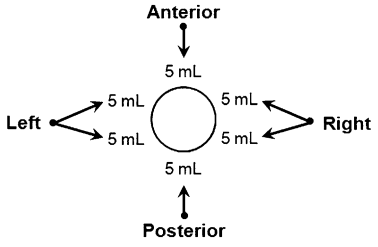

FIG. 2. Study drug infiltration technique: Study drug was administered via infiltration in a fanlike fashion outside of the anal sphincter (*center circle*); 10 mL was injected on the left side, 10 mL on the right side, 5 mL anteriorly, and 5 mL posteriorly. Reprinted with permission from Stephen R. Gorfine, M.D., Erol Onel, M.D., Gary Patou, M.D., and Zoran V. Krivokapic, M.D., Ph.D., Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial, Diseases of the Colon & Rectum, Vol. 54, Issue 12, pp 1552–1559, Copyright © The American Society of Colon & Rectal Surgeons, Inc. 2011.

Outcome Assessments

Efficacy outcome measures included: 1) cumulative pain score reflected by area under the curve (AUC) for NRS scores through 12, 24, 36, 48, 60, 72, 84, and 96 hours after administration of study medication; 2) pain intensity during BM (NRS-BM); 3) time to first BM; 4) proportion of patients receiving no postsurgery rescue opioid medication; 5) time to first use of postsurgical opioid medication; 6) total postsurgical consumption of rescue opioid medication; 7) blinded care provider's satisfaction with postsurgical analgesia; 8) QOL assessed using the EQ-5D™ 20-cm vertical scale; 9) date of return to work or normal daily activities through study Day 30; and 10) discharge readiness using the Modified Postanesthesia Discharge Scoring System[18] recorded at 1, 2, and 3 hours after surgery. Discharge readiness was defined as a Modified Postanesthesia Discharge Scoring System score ≥9. Although the study was designed to assess efficacy measurements through 96 hours postsurgery, the efficacy results at 72 hours are highlighted here to remain consistent with the rest of the Phase 2 and 3 studies in the LB clinical development program, where LB was administered via wound infiltration in patients undergoing hernia repair, total knee arthroplasty, hemorrhoidectomy, bunionectomy, or breast augmentation.

Safety outcome measures included AEs (defined as any AEs that occurred after the first administration of study medication) and changes in vital signs during the course of the study. Mild AEs were those that were easily tolerated, caused minimal discomfort, and did not interfere with daily activities. Moderate AEs were those that were discomforting and interfered with normal everyday activities. Severe AEs were those that prevented normal everyday activities. Serious AEs included AEs that were life-threatening, resulted in a new hospitalization or prolonged an existing hospitalization, caused a significant disability or incapacity, or were otherwise medically significant.

Data Analysis

Power calculations were based on results from a Phase 2 hernia study.[19] A sample size of 25 in each group will have 80 per cent power to detect a 30 per cent difference in mean AUC of pain intensity scores on a 10-mm visual analogue scale assuming a common standard deviation of 1350 using a two-group *t* test with a 0.05 two-sided significance level. The study was not originally powered to take multiple comparisons into account. However, a Bonferroni adjustment was made *post hoc* for each endpoint.[20] All confidence intervals reported are Bonferroni-adjusted, unless otherwise stated. Therefore, all tests were declared statistically significant if the calculated P value was ≤ 0.017.

The safety population included all patients who received study medication. Safety analyses were based on treatment actually received. The efficacy analysis set included all patients in the safety population who underwent the planned surgical procedure and who had at least 1 postbaseline NRS pain score. Efficacy analyses were performed on the efficacy analysis set and were based on the treatment group to which patients were randomized regardless of treatment received.

The AUC NRS assessments were calculated using the trapezoidal method and analyzed using an analysis of variance method with treatment group as the main effect. This same model was used to test for treatment differences for all continuous variables. For the analysis of total postsurgical consumption of rescue opioid medication, all opioids were converted to an equianalgesic parenteral morphine amount using standard conversion factors[21] and a log transformation was applied before analysis. Fisher's exact test was used to compare between-group differences in the discharge readiness, proportion of patients who received no postsurgical rescue opioids, and time to return to work or normal activities. Comparisons of time to first use of postsurgical opioid medication were made using log-rank tests.

Adverse events were summarized by treatment group. The United States Food and Drug Administration has accepted incidences of constipation, nausea, pruritus, and vomiting as an appropriate representation of opioid-related AEs.[22] *Post hoc*, between-group comparisons were made in the current study as well to assess differences in the incidence of these opioid-related AEs.

Results

A total of 105 patients were enrolled in this study (48 in Cohort 1; 57 in Cohort 2). Of these, five were randomized but not dosed; 100 patients received the study drug in the LB 66-mg (n = 24), 199-mg (n = 25), and 266-mg (n = 25), and bupivacaine HCl (n = 26) groups. Patients were enrolled at 9 study centers; 3 centers each enrolled more than 10 patients and the remaining 6 centers each enrolled less than 10 patients. One patient who was randomized to LB 66 mg inadvertently received bupivacaine HCl 75 mg. This patient was included in the LB 66-mg group for the efficacy analyses and in the bupivacaine HCl 75-mg group for safety analyses. Ninety-seven patients (97%) completed the entire study. Two patients, one in the LB 66-mg group and one in the bupivacaine HCl group, were lost to follow-up and one patient in the bupivacaine HCl group withdrew consent. Patient demographics and baseline characteristics are summarized in Table 1.

Efficacy

Pain intensity, as reflected by the mean cumulative pain scores (AUC of NRS), was significantly lower in the LB 199- and 266-mg groups compared with the bupivacaine HCl group through 72 hours after administration of study medication (Fig. 3). The greatest between-group difference occurred in the LB 266-mg group compared with the bupivacaine HCl 75-mg group. Differences in cumulative pain scores remained statistically significant for the LB 199- and 266-mg groups compared with bupivacaine HCl through 96 hours [LB 66 mg, 95% confidence interval (CI) for difference *vs* bupivacaine HCl, –302, 11, $P = 0.023$; 199 mg, 95% CI for difference, –363, –52, $P = 0.001$; 266 mg, 95% CI for difference, –373, –60, $P < 0.001$]. Pain intensity scores at first BM (NRS-BM) were significantly lower in the LB 199-mg [mean standard deviation (SD), 4.5 (3.0), $P = 0.01$] and 266-mg [mean (SD), 4.1 (2.1), $P = 0.003$] groups compared with the bupivacaine group HCl [mean (SD), 6.7 (2.7)]. Average NRS-BM scores in the three LB groups were not statistically different than scores in the bupivacaine HCl group. The mean time to first BM ranged from 55 to 64 hours across the four treatment groups with no significant differences observed. A smaller proportion of patients in each of the three LB groups required rescue opioid medication compared with the bupivacaine HCl group between

TABLE 1. *Patient Demographics and Baseline Characteristics (Safety Population)*

	LB			Bupivacaine HCl*
	66 mg (n = 24)	199 mg (n = 25)	266 mg (n = 25)	75 mg (n = 26)
Age, years, mean (SD)	42 (11)	42 (11)	46 (11)	44 (11)
Gender, n (%)				
Male	17 (71)	16 (64)	22 (88)	15 (58)
Female	7 (29)	9 (36)	3 (12)	11 (42)
Race, n (%)				
White	21 (88)	25 (100)	24 (96)	24 (92)
Black/African American	3 (13)	0	1 (4)	2 (8)
Weight, kg, mean (SD)	85 (25)	77 (19)	82 (16)	80 (16)
Height, cm, mean (SD)	173 (11)	171 (9)	174 (6)	171 (10)
ASA Physical Status Classification, n (%)				
1–2	18 (75)	23 (92)	22 (88)	19 (73)
3–4	4 (17)	2 (8)	2 (8)	2 (8)
Not reported	2 (8)	0	1 (4)	5 (19)

* Bupivacaine HCl 75 mg with epinephrine 1:200,000.
SD, standard deviation; ASA, American Society of Anesthesiologists.

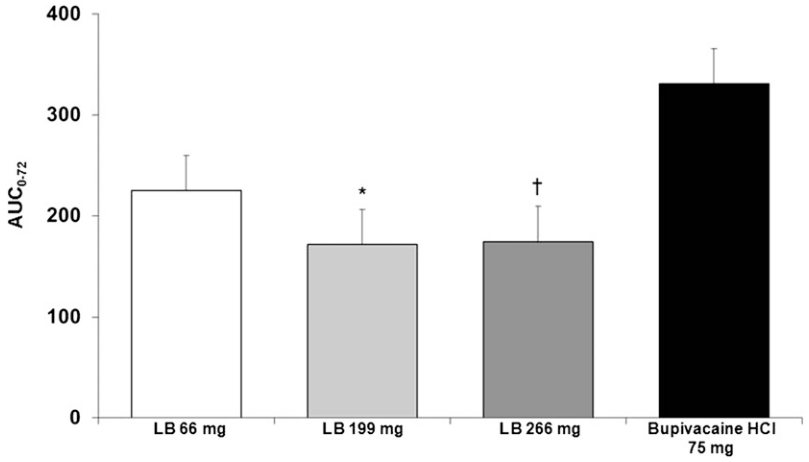

FIG. 3. Mean area under the curve ± SEM for the postoperative numeric pain intensity scores (NRS) from 0–72 hours in the bupivacaine HCl and LB treatment groups. *$P = 0.002$ *versus* bupivacaine HCl 75 mg; †$P = 0.002$ *versus* bupivacaine HCl 75 mg.

8 and 72 hours after surgery. In the LB 266-mg group, eight of 25 patients (32%) were opioid-free through 72 hours postsurgery *versus* two of 25 (8%) in the bupivacaine HCl group ($P = 0.074$). The between-group differences did not reach statistical significance for any of the LB groups compared with bupivacaine HCl at any time point.

The median (range) time to first use of postsurgical rescue opioid medication was 8 (0.3–96.0) hours in the bupivacaine HCl group compared with 9 (0.1–96.0) hours in the LB 66-mg group, 11 (0.2–96.0) hours in the 199-mg group, and 19 (0.1–96.0) hours in the 266-mg group ($P = 0.005$ for the 266-mg group *vs* bupivacaine HCl). To further analyze the pharmacodynamics of LB, different AUC time intervals were subsequently examined. The total amount of rescue opioid medication used through 96 hours after surgery is summarized in Fig. 4. The differences in the total amount of rescue opioid medication used were statistically significant for the LB 266-mg group compared with bupivacaine HCl 75 mg through 48, 60, 72, 84, and 96 hours after surgery. The ratios of LB 266 mg to bupivacaine HCl at these time points were 0.39 ($P = 0.015$), 0.037 ($P = 0.011$), 0.34 ($P = 0.007$), 0.32 ($P = 0.004$), and 0.31 ($P = 0.004$). A *post hoc* analysis was conducted to assess the difference in opioid consumption from 0 to 12 hours postdose compared with opioid consumption from 12 to 72 hours postdose. During the first 12 hours postdose, when both the LB and bupivacaine HCl formulations are presumed to be active, the total amount of rescue opioid medication used was not statistically different across the treatment groups. Between 12 and 72 hours postinfiltration, when LB is presumed to be active but bupivacaine HCl is not, a statistically significantly lower total amount of opioids were used in the LB 266-mg group (3.7 *vs* 10.2 mg, $P = 0.019$). Because this was a *post hoc* analysis, the Bonferroni correction was not applied.

Mean (SD) scores for the blinded care provider's satisfaction with postsurgical analgesia assessment were

6 (2), 7 (2), and 7 (2) in the LB 66-, 199-, and 266-mg groups, respectively, compared with 6 (2) in the bupivacaine HCl group ($P = 0.03$ for LB 266 mg *vs* bupivacaine HCl). At baseline, the EQ-5D™ QOL mean (SD) assessment scores were 72 (18), 74 (18), 68 (18), and 67 (24) in the LB 66-mg, 199-mg, 266-mg, and bupivacaine HCl groups, respectively. Significant improvement was observed in the mean scores for the LB 266-mg group compared with the bupivacaine HCl group at 48 and 72 hours after administration of study medication ($P = 0.006$ and < 0.001 at 48 and 72 hours, respectively). By the end of the study, 96 per cent of patients treated with LB 266 mg had returned to work or normal daily activities compared with 83 per cent of the bupivacaine HCl patients ($P = 0.19$). There were no significant differences between the treatment groups in terms of the number of patients who met the discharge criteria at 1, 2, and 3 hours after surgery.

Safety

A total of 26 patients (26%) reported at least one AE. In total, 15 (20%) treated with LB and 14 (42%) treated with bupivacaine HCl experienced AEs. Adverse events are summarized in Table 2. The majority of AEs were mild or moderate in severity. Constipation, nausea, and

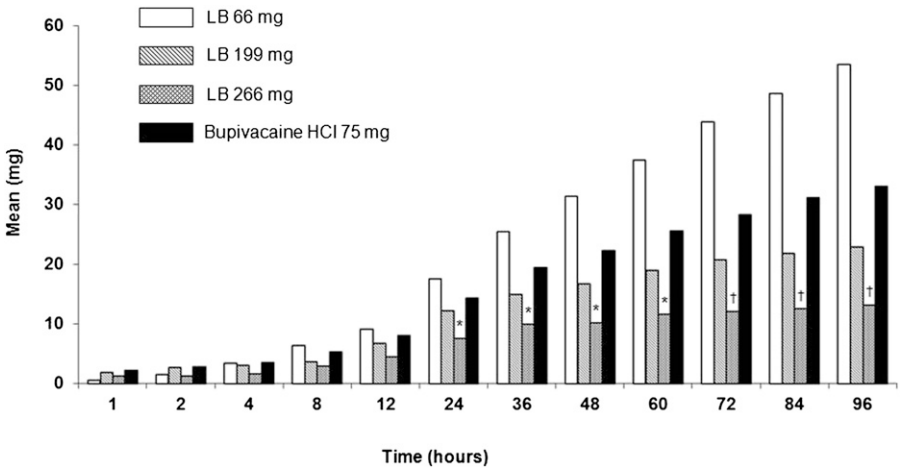

FIG. 4. Total consumption of rescue opioid medication (efficacy analysis set). All opioids have been converted to equianalgesic parenteral morphine amounts (mg). Means were obtained using an analysis of variance model with treatment as the main effect. *$P < 0.05$ *versus* bupivacaine HCl 75 mg; †$P < 0.01$ *versus* bupivacaine HCl 75 mg.

TABLE 2. *Summary of Adverse Events (Safety Population)**

	LB			Bupivacaine HCl†
	66 mg (n = 24) n (%)	199 mg (n = 25) n (%)	266 mg (n = 24) n (%)	(n = 26) n (%)
Number of patients (%) with ≥ 1 AE‡	7 (29.2)	7 (28.0)	1 (4.0)	11 (42.3)
Gastrointestinal AEs	7 (29.2)	7 (28.0)	0	9 (34.6)
Most common AEs (≥3%)				
Constipation	3 (12.5)	5 (20.0)	0	4 (15.4)
Nausea	3 (12.5)	4 (16.0)	0	3 (11.5)
Vomiting	1 (4.2)	3 (12.0)	0	3 (11.5)
Flatulence	1 (4.2)	0	0	1 (3.8)
Rectal hemorrhage	1 (4.2)	0	0	1 (3.8)
Pruritus	0	0	1 (4.0)	1 (3.8)
Abdominal distension	1 (4.2)	0	0	0
Dyspepsia	0	0	0	1 (3.8)
Hematochezia	0	0	0	1 (3.8)
Infrequent bowel movements	0	0	0	1 (3.8)
Nasopharyngitis	0	0	1 (4.0)	0
Rash	1 (4.2)	0	0	0
Skin irritation	0	0	0	1 (3.8)
Urinary tract infection	0	0	0	1 (3.8)

* Patients from Cohorts 1 and 2 at the same dose/treatment have been combined.
† Bupivacaine HCl 75 mg with epinephrine 1:200,000.
‡ If a patient experienced more than one episode of a particular adverse event, the patient was counted only once for the event.

vomiting were the most frequently reported AEs across all treatment groups. One patient in the LB 66-mg group reported a serious AE (rectal hemorrhage) that was not considered related to study medication by the study investigator. This event resolved after application of two small sutures. One patient in the LB 266-mg group reported a mild AE of pruritus that was considered by the investigator to be related to study medication; no other AEs were considered related to study medication. No bowel incontinence was reported during the study and no patients discontinued participation in the study due to AEs. The reported incidence of opioid-related AEs (constipation, nausea, vomiting, pruritus) was 4 per cent in the LB 266-mg group compared with 35 per cent in the bupivacaine HCl group ($P = 0.006$).

Discussion

As reflected in multiple clinically relevant efficacy measures (*e.g.,* cumulative pain scores, time to first use of opioid medication, total amount of opioid medication consumed postsurgery), extended-release LB 266 mg was statistically superior to bupivacaine HCl for up to 96 hours in this population of hemorrhoidectomy patients. This study was designed to mimic clinical practice with the differences between LB and bupivacaine HCl assessed against a background of standard-of-care multimodal therapy for which patients received both concomitant ketorolac and acetaminophen or paracetamol.[5] This was the most stringent setting in which to test the additional benefits of a longer-acting bupivacaine delivered over 72 to 96 hours by the DepoFoam technology.

Greater reductions in cumulative pain score and postsurgical opioid usage were observed with increasing doses of LB in this study, and LB 266 mg was shown to be statistically more effective than bupivacaine HCl as reflected in cumulative pain scores, postsurgical opioid consumption, and consequent opioid-related AEs (Fig. 5). Opioid-related AEs are associated with increased costs to the health care system. Strategies to reduce opioid-related AEs contribute to improving the patient's quality of recovery and may reduce hospital costs. Subsequent analysis of total opioid consumption over different periods of time (*e.g.,* AUC from 0 to 12 and 12 to 72 hours) showed that the superior efficacy of LB over bupivacaine HCl was largely explained by the greater consumption of opioid rescue medication in the bupivacaine HCl arm after 12 hours, consistent with both the short duration of action of bupivacaine HCl and the prolonged duration of therapeutic effect of LB. These results are consistent with results observed in previous studies assessing perioperative administration of bupivacaine via continuous local infusion with elastomeric pumps.[23, 24] However, the previous studies lacked an active comparator arm, and some patients were excluded from analyses due to inadvertent catheter dislodgement or breakage.

In the current study, LB was well tolerated. There was a marked decrease in the reported incidence of AEs in the LB 266-mg group (one patient reported pruritus; no other AEs were reported in this group) compared with the bupivacaine HCl group (42.3% reported any AE, 34.6% reported opioid-related AEs). This differential in AE incidence is presumably due to the decreased opioid requirement and consumption in the LB 266-mg group. Based on the results of this exploratory dose-ranging study, it seems the LB 266-mg dose level has the potential to enhance analgesia during the acute postsurgical period in hemorrhoidectomy patients

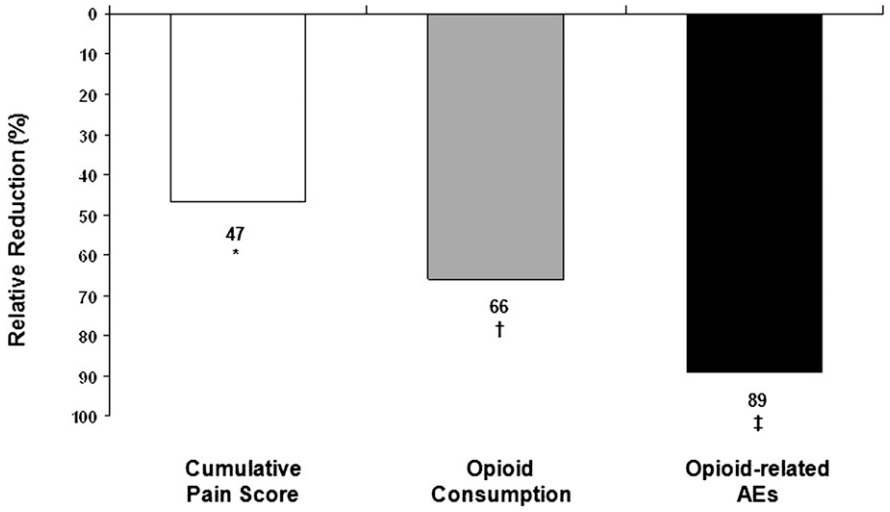

FIG. 5. Relative reduction (%) in cumulative pain score [area under the curve of numeric pain intensity scores (NRS) from 0–72 hours], postsurgical opioid consumption, and opioid-related adverse events for LB 266 mg compared with bupivacaine HCl. *$P = 0.002$ *versus* bupivacaine HCl 75 mg; †$P = 0.007$ *versus* bupivacaine HCl 75 mg; ‡$P = 0.007$ *versus* bupivacaine HCl 75 mg.

without increasing incidence of opioid-related AEs; however, larger clinical studies are warranted.

The major limitations and deficiencies in our study include the following: First, there was a relatively small, healthy population of patients in each treatment arm (n = ~25) who were without substantial concomitant medical conditions that may be encountered in clinical practice; indeed, patients at high risk for poor outcomes for opioid-related AEs (elderly, opioid intolerant, obese, sleep apnoeic) were excluded from participating in the study. Second, the patient population ranged in age from 21 to 69 years and therefore these findings may differ in very young and very old (geriatric) patients. Third, the general anesthetic technique was not rigorously standardized at all participating centers in this multicenter, multinational study, and last, the use of prophylactic and rescue antiemetic drugs was left to the discretion of the investigator at each of the study sites.

In summary, liposome bupivacaine has the potential to offer important clinical advantages over bupivacaine HCl for pain relief in the setting of hemorrhoidectomy, including a longer duration of analgesia, less use of opioid analgesic medications, and fewer opioid-related AEs. Further clinical studies are needed to better define the clinical role of this new local anesthetic in the future practice of perioperative pain management.

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