ORIGINAL CONTRIBUTION

# Bupivacaine Extended-Release Liposome Injection for Prolonged Postsurgical Analgesia in Patients Undergoing Hemorrhoidectomy: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

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**BACKGROUND:** Bupivacaine extended-release liposome injection is a novel formulation of bupivacaine designed to achieve long-acting postoperative analgesia.

**OBJECTIVE:** The aim of this study was to compare the magnitude and duration of postoperative analgesia from a single dose of bupivacaine extended-release injection with placebo administered intraoperatively in patients undergoing hemorrhoidectomy.

**DESIGN:** This evaluation was a multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 3 study.

**SETTINGS:** Data were obtained from 13 centers in the Republic of Georgia, Poland, and Serbia.

**PATIENTS:** Included in this study were patients aged 18 to 86 years undergoing excisional hemorrhoidectomy.

**INTERVENTIONS:** All patients received either a single dose of bupivacaine extended-release 300 mg or placebo administered intraoperatively via wound infiltration.

**MAIN OUTCOME MEASURE:** The cumulative pain score was assessed by measurement of the area under the curve of pain intensity through 72 hours after study drug administration.

**RESULTS:** One hundred eighty-nine patients were randomly assigned and treated; 186 completed the study. Pain intensity scores were significantly lower in the bupivacaine extended-release group in comparison with the group receiving placebo (141.8 vs 202.5, $P < .0001$). More patients in the bupivacaine extended-release group remained opioid free from 12 hours (59%) to 72 hours (28%) after surgery compared with patients receiving placebo (14% and 10%; $P < .0008$ through 72 h). The mean total amount of opioids consumed through 72 hours was 22.3 mg and 29.1 mg in the bupivacaine extended-release and placebo groups ($P \leq .0006$). The median time to first opioid use was 14.3 hours in the bupivacaine extended-release group vs 1.2 hours in the placebo group ($P < .0001$). A greater proportion of patients in the bupivacaine extended-release group were satisfied with their postsurgical analgesia (95% vs 73%, $P = .0007$) than in the placebo group.

**CONCLUSIONS:** Bupivacaine extended-release demonstrated a statistically significant reduction in pain through 72 hours, decreased opioid requirements, delayed time to first opioid use, and improved patient satisfaction compared with placebo after hemorrhoidectomy.

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**KEY WORDS:** Liposomal bupivacaine; Postoperative pain; Postsurgical pain; Hemorrhoidectomy; Opioid sparing; Patient satisfaction.

Approximately 70 million surgical procedures are performed annually in the United States; approximately half are performed as inpatient procedures.[1,2] Most patients report moderate, severe, or extreme pain[3,4] during the first few days after surgery,[5] and an estimated 15% to 45% experience chronic postsurgical pain.[6,7] Effective postsurgical pain control is critical to patient recovery, and can contribute to improved healing, faster patient mobilization, shortened hospital stays, and reduced health care costs.[8]

Multimodal techniques for perioperative pain management are recommended to maximize pain relief, lower the risk of adverse events (AEs), and improve patient outcomes.[8,9] The administration of local anesthetics (eg, bupivacaine) via wound infiltration is a common, effective practice for postsurgical pain management.[10,11] However, it provides relatively brief analgesia, lasting at best about 12 hours.[11–13] Because effective postoperative analgesia is often required for at least 72 hours, delivery systems (eg, elastomeric infusion pumps) may be used to extend the duration of action of locally administered anesthetics and thereby decrease opioid requirements.[14] However, these delivery systems may involve an indwelling catheter, which introduces inconvenience and the associated risks of infection and dislodgment, thereby limiting widespread adoption. Thus, the use of systemic opioids remains a mainstay of postoperative treatment, especially in the outpatient setting. Although they are effective, opioids have drawbacks that include respiratory depression, hypotension, nausea, vomiting, central nervous system depression, pruritus, and constipation.[15,16] Concerns about opioid-related complications can result in substantial undertreatment of acute pain and inappropriate postsurgical pain management.[17–25]

A local analgesic providing adequate postsurgical pain relief for a longer duration than currently available agents could be a useful therapeutic option for the management of postsurgical pain. DepoFoam bupivacaine (bupivacaine extended-release liposome injection, EXPAREL; Pacira Pharmaceuticals, Inc, Parsippany, NJ) was designed to achieve prolonged pain relief with single-dose administration intraoperatively via wound infiltration. DepoFoam bupivacaine consists of microscopic, spherical, and multivesicular liposomes (the DepoFoam drug delivery system). Each liposome particle is composed of a honeycomb-like structure of numerous internal aqueous chambers containing encapsulated bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. Bupivacaine is released from the liposome particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period.

The primary objective of this study was to investigate the magnitude and duration of analgesia provided by a single dose of DepoFoam bupivacaine 300 mg administered intraoperatively for postsurgical pain compared with placebo (0.9% sodium chloride) in patients undergoing hemorrhoidectomy under general anesthesia.

## MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled, parallel-group phase 3 study evaluated the efficacy and safety of DepoFoam bupivacaine compared with placebo for postsurgical pain relief in patients undergoing 2- or 3-column excisional hemorrhoidectomy. The study was conducted at 13 study centers in the Republic of Georgia, Poland, and Serbia from May to August 2009 (US National Institutes of Health Clinical Trials Identifier: NCT00890721), 12 of which enrolled at least 1 patient. The study was conducted in compliance with the Declaration of Helsinki and its amendments and in accordance with good clinical practice.[26,27] The study protocol and informed consent forms were approved by national regulatory authorities in each country and an independent ethics committee at each study center. Written informed consent was obtained from all patients before any study procedures were performed.

### Patients

Study participants were men and nonpregnant women aged 18 years or older scheduled to undergo 2- or 3-column excisional hemorrhoidectomy under general anesthesia (Milligan-Morgan technique). Patients were required to have an ASA physical status classification of 1, 2, or 3. Female patients had to be postmenopausal, surgically sterile, or willing to use acceptable means of contraception for at least 30 days after surgery.

Patients were excluded if they had concurrent or recent medical conditions that could interfere with study participation, including history of hepatitis, alcohol/substance abuse, uncontrolled psychiatric disorders, known allergy, or contraindication to amide-type local anesthetics, opioids, or propofol. Patients were also excluded if they had a body weight of less than 50 kg, had participated in another study involving an investigational medication within the prior 30 days, or were taking analgesics (ie, nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids), antidepressants, or glucocorticoids within the 3 days before surgery.

### Study Design

Screening procedures were performed within 30 days of the patient's scheduled procedure. During the screening visit, informed consent was obtained, study eligibility was confirmed, and medical/surgical history, vital sign measurements, drug/alcohol screening, and clinical laboratory tests, including Chem-12 and complete blood counts, were obtained. Patients were also trained on the pain assessment tools used during the study.

Patients returned to the study center within 24 hours of the scheduled surgery for preoperative procedures at

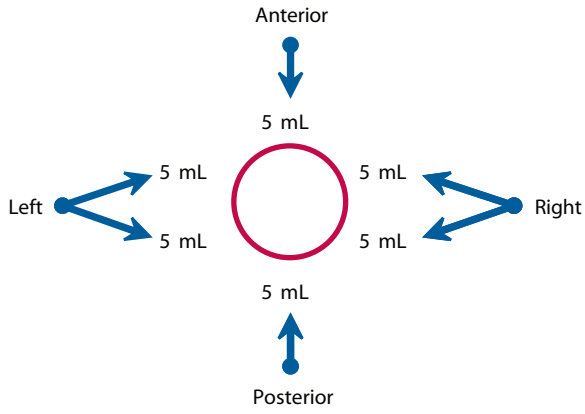


**FIGURE 1.** Study drug infiltration technique. Study drug was administered via infiltration in a fanlike fashion outside of the anal sphincter (center circle); 10 mL was injected on the left side, 10 mL on the right side, 5 mL anteriorly, and 5 mL posteriorly.

baseline, including eligibility reconfirmation and review of patient history. Physical examinations were conducted and assessments of patients' pain intensity at rest were also obtained. Pain intensity at rest was measured using a validated 11-point numeric rating scale (NRS; 0 = no pain and 10 = worst possible pain).[28,29] Patients were randomly assigned in a blinded manner to receive DepoFoam bupivacaine 300 mg/30 mL or placebo (0.9% sodium chloride 30 mL) in a 1:1 ratio.

All assessments conducted after baseline were timed from the start of study drug infiltration (day 1). Surgical procedures were conducted under general anesthesia and patients were monitored during surgery per the standard of practice at each study center. Patients, surgical teams, and study personnel conducting study-related assessments were blinded to assigned study drug. Study drug was injected at the end of surgery in 5-mL increments using a standard anal block procedure with a moving-needle technique, performed by infiltrating the perianal tissues (just outside the external sphincter) in a fanlike fashion around the anus (Fig. 1). Total volume of study drug used for infiltration was 30 mL. The use of fentanyl was permitted during surgery, but the intraoperative use of all other analgesics or local anesthetics was prohibited, unless needed to treat an AE.

Patients remained at the study center for at least 72 hours after surgery. Postsurgical analgesia for breakthrough pain consisted of morphine sulfate 10 mg administered intramuscularly every 4 to 6 hours as needed for the first 72 hours of the postsurgical period. No other rescue medications were permitted during this period unless the patient's pain could not be effectively managed with intramuscularly administered morphine. In these cases, only pure opioid products were permitted as substitutions for morphine. Patients were allowed to receive parenteral antiemetic medications and low-dose aspirin for cardiac protection/platelet inhibition if needed. The use of topical or intrarectal medications, as well as analgesic adjuvants (eg, clonidine, benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, and nonpharmacologic methods of pain management) were prohibited for 72 hours after study drug administration. Patients were instructed to eat a high-fiber diet and drink plenty of noncaffeinated liquids. Stool softeners and laxatives were administered as necessary, and sitz baths were prescribed at the discretion of the surgeon during the week after surgery.

Occurrences and duration of AEs and use of all concomitant medications were recorded throughout the 72-hour postsurgical period. Pain intensity was measured using the NRS at the end of general anesthesia and before the first dose of morphine (if applicable) and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery. Patients completed the Brief Pain Inventory (BPI) at 24 and 72 hours after surgery, and satisfaction with postsurgical analgesia was assessed at 24 and 72 hours by the use of a 5-point categorical scale where responses ranged from "extremely dissatisfied" to "extremely satisfied." Patients returned to the study site at days 8 and 30 for follow-up assessments.

### Outcome Measures

The primary efficacy measure was pain relief as assessed by the cumulative pain score as reflected in the NRS area under the curve through 72 hours after study drug administration ($AUC_{0-72}$). Other efficacy measures included the proportion of patients who received no supplemental opioid rescue medication; the total amount (milligrams) of opioid rescue medication consumed through 12, 24, 36, 48, 60, and 72 hours after surgery; the time to first postsurgical use of opioid rescue medication; BPI assessment at 24 hours, 72 hours, and day 30 after surgery; and the patient's rating of satisfaction with postsurgical analgesia. Treatment-emergent AEs, defined as any AE occurring after administration of study drug, were recorded from baseline through time of discharge, and at follow-up visits on days 8 and 30. Other safety assessments included clinical laboratory tests and vital sign measurements and caregiver's satisfaction with wound healing at day 30, which was rated on a 10-point numerical scale (0 = completely satisfied with wound healing; 10 = completely unsatisfied with wound healing).

### Statistical Analysis

A sample size of approximately 180 randomly assigned patients was planned (90 patients in each treatment group). The sample size estimate was based on results from a phase 2 active-control hemorrhoidectomy study where the mean (SD) $AUC_{0-72}$ values were 331 (175) and 175 (173) in the bupivacaine HCl and DepoFoam bupivacaine groups. All statistical tests were performed using SAS Software version 9.1 against a 2-sided alternative hypothesis at a significance level of $P \leq .05$.

Safety analyses were based on the actual treatment received for the safety population, which included all randomly selected patients who received any amount of study drug. Efficacy analyses for the full analysis set were based on randomized treatment, regardless of treatment received. The full analysis set included all patients in the safety population who underwent the surgical procedure and had sufficient data to compute the $AUC_{0-72}$ (at least 2 NRS pain intensity scores within 72 h after surgery).

For the calculation of AUC, data were imputed with the use of the windowed worst observation carried forward plus last observation carried forward method. For subjects who used opioid rescue medication, their NRS scores recorded within the window of controlled type of rescue medication (one half-life of the rescue medication) were replaced by the "worst" observation (ie, the highest score before taking their first rescue medication). Missing scores were replaced in 1 of 3 ways: 1) by the median score from other subjects at the same time point in the same treatment group if before the first nonmissing score; 2) by last observation carried forward if after the last nonmissing score; and 3) by linear interpolation if between 2 nonmissing scores. The mean $AUC_{0-72}$ for DepoFoam bupivacaine and placebo were calculated by the use of the trapezoidal method. These values were compared using an ANOVA model with treatment and country as the main effects. A Cochran-Mantel-Haenszel test was used, adjusting for country, when comparing DepoFoam bupivacaine and placebo with respect to percentage of patients who received no opioid rescue medications and patient's satisfaction with postsurgical analgesia.[30] For total postsurgical consumption of opioid rescue medications, all opioid doses were converted to an equianalgesic parenteral morphine amount using standard conversion factors.[31] An ANOVA model with treatment and country as the main effects on log-transformed data was used to compare treatment groups. Log-rank tests were used to compare DepoFoam bupivacaine and placebo with respect to the distribution of time to first postsurgical use of opioid medication. Between-group differences at baseline in answers to BPI questions based on rating scales were analyzed by the use of an ANOVA model with treatment and country as the main effects; an analysis of covariance model was then used for postsurgical BPI assessments with baseline response as the covariate.

All treatment-emergent AEs were classified by system organ class and preferred term before analysis and summarized by treatment group. No formal statistical

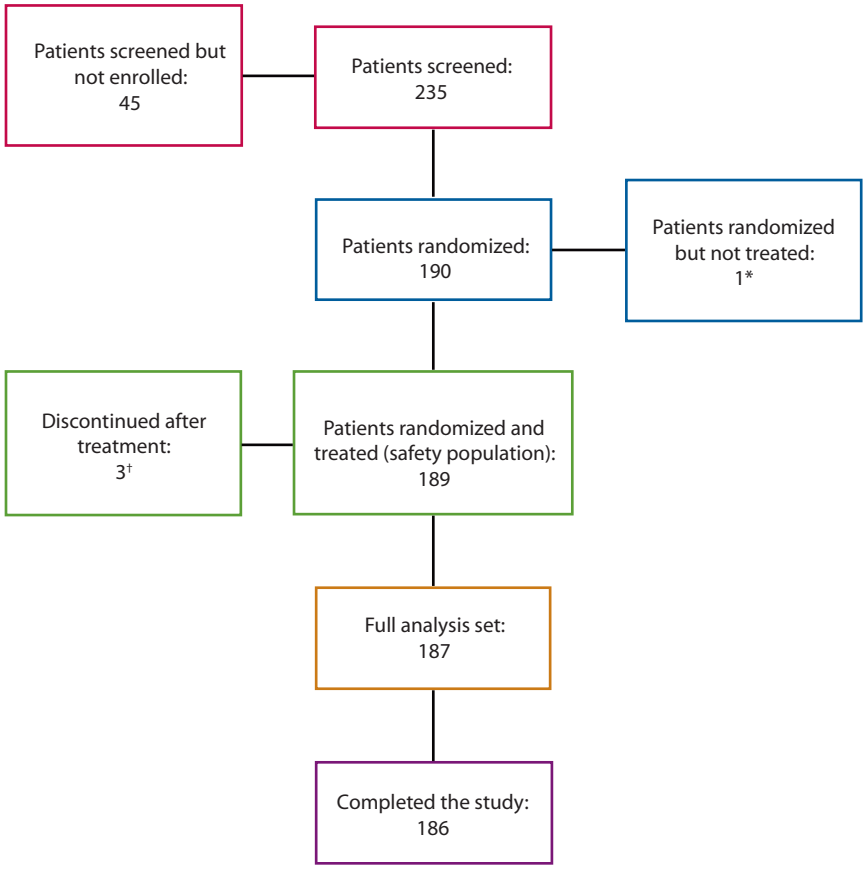


**FIGURE 2.** Patient disposition. *Patient discontinued due to atrial-ventricular block. †One patient in the DepoFoam bupivacaine group and 2 patients in the placebo group withdrew consent.

**TABLE 1.** Patient demographics and baseline characteristics (safety population)

| | *DepoFoam bupivacaine 300 mg (n = 95)* | *Placebo (n = 94)* |
|---|---|---|
| Age (y), mean (SD) | 48.0 (12.2) | 48.7 (11.9) |
| Sex | | |
| Male | 63 (66.3) | 67 (71.3) |
| Female | 32 (33.7) | 27 (28.7) |
| ASA physical status classification | | |
| 1 | 57 (60.0) | 49 (52.1) |
| 2 | 36 (37.9) | 42 (44.7) |
| 3 | 2 (2.1) | 3 (3.2) |
| Weight (kg), mean (SD) | 76.3 (15.0) | 78.7 (13.4) |
| Height (cm), mean (SD) | 172.3 (8.5) | 174.2 (9.4) |
| BMI (kg/m$^2$), mean (SD) | 25.5 (3.9) | 25.9 (3.9) |
| Milligan-Morgan technique | | |
| Open (classic) | 78 (82.1) | 78 (83.0) |
| Semiopen (modified) | 17 (17.9) | 13 (13.8) |
| Missing | 0 | 3 (3.2) |

Data are numbers of patients with percentages in parentheses unless otherwise noted.

comparisons were performed for AEs. For caregiver's overall satisfaction with patient's wound healing, between-group differences were compared by the use of ANOVA with treatment and country as main effects.

## RESULTS

A total of 189 patients were randomly assigned and received study drug, and 186 patients completed the study (Fig. 2). Patient demographics and baseline characteristics are shown in Table 1.

### Efficacy

As reflected in the primary efficacy measure, pain intensity was significantly less through 72 hours after surgery following treatment with DepoFoam bupivacaine (least squares (LS) mean (SE) $AUC_{0-72}$ 141.8 (10.7), $P < .0001$) compared with placebo (LS mean (SE) $AUC_{0-72}$ 202.5 (10.7)) (Fig. 3). The mean (SD) $AUC_{0-72}$ values also favored DepoFoam bupivacaine when patients were stratified by country: Republic of Georgia, 108.2 (94.9) vs 234.0 (102.6); Poland, 162.4 (116.3) vs 185.0 (89.2); and Serbia, 162.2 (86.0) vs 180.3 (110.6) for the DepoFoam bupivacaine and placebo groups.

The proportion of patients who received no opioid rescue medication was significantly greater in the DepoFoam bupivacaine groups ($P < .0008$) through every measured time point beginning at 12 hours through 72 hours after administration of study drug (Fig. 4). The mean total amount of opioid rescue medication (morphine equivalents) consumed was significantly lower in the DepoFoam bupivacaine group ($P \leq .0006$) for every measured time point through 72 hours after study drug administration

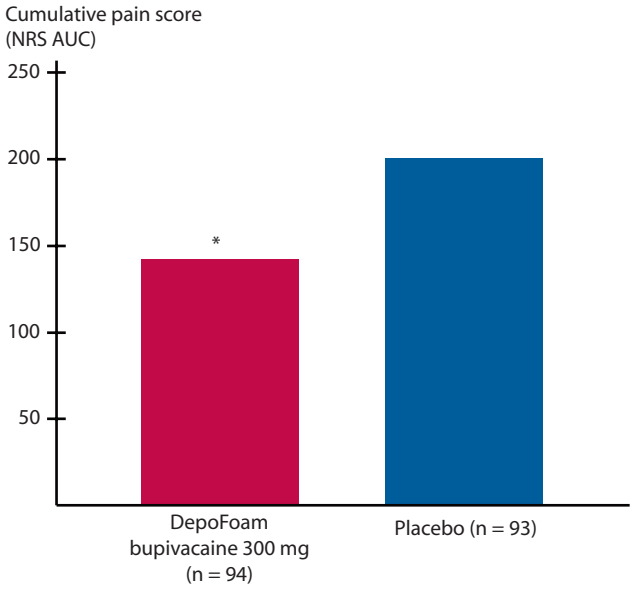


**FIGURE 3.** Cumulative pain score (NRS AUC) through 72 hours after administration of study drug (full analysis set). *$P < .0001$. NRS = numeric rating scale; AUC = area under the curve.

(Table 2). The median time to first use of opioid rescue medication after surgery was 14 hours 20 minutes in the DepoFoam bupivacaine group compared with 1 hour 10 minutes in the placebo group ($P < .0001$). The Kaplan-Meier analysis for time to first opioid rescue medication use is presented in Figure 5. On the assessment of BPI at 24 hours, patients in the DepoFoam bupivacaine group reported less pain and less pain-related interference with general activities, mood, walking, work, social relations, and enjoyment of life than patients who received placebo. At the 72-hour BPI assessment, patients in the DepoFoam bupivacaine group reported less pain-related interference with mood, walking, and work than patients in the placebo group. As expected, BPI scores were similar across treatment groups by the time the day 30 assessment was obtained. The distribution of responses on the assessment of

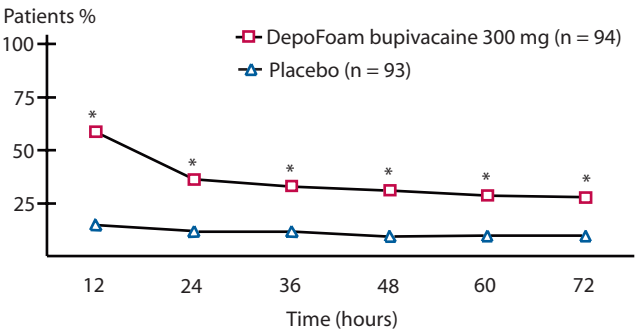


**FIGURE 4.** Percentage of patients who received no opioid rescue medication through 72 hours (full analysis set). *$P < .0008$.

**TABLE 2.** Mean (SD) total amount of opioid rescue medication (morphine equivalents) consumed (full analysis set)[a]

| *Time from 0 through* | *DepoFoam bupivacaine 300 mg (n = 94)* | *Placebo (n = 93)* |
|---|---|---|
| 12 h postdose | 6.2 (8.2)[b] | 14.7 (10.7) |
| 24 h postdose | 11.3 (11.8)[b] | 20.0 (13.5) |
| 36 h postdose | 15.7 (15.7)[b] | 23.3 (15.9) |
| 48 h postdose | 17.2 (17.2)[b] | 25.4 (17.7) |
| 60 h postdose | 21.2 (20.2)[c] | 28.2 (20.3) |
| 72 h postdose | 22.3 (21.0)[d] | 29.1 (20.7) |

[a]*P* values calculated from an ANOVA model with treatment and country as main effects on natural log-transformed opioid amount. Amounts are presented in the original, nontransformed scale.
[b]$P < .0001$ compared with placebo.
[c]$P = .0003$ compared with placebo.
[d]$P = .0006$ compared with placebo.

**TABLE 3.** Summary of treatment-emergent adverse events

| | *DepoFoam bupivacaine 300 mg (n = 95)* | *Placebo (n = 94)* | *Overall (n = 189)* |
|---|---|---|---|
| Patients with ≥1 AE[a] | 16 (16.8) | 17 (18.1) | 33 (17.5) |
| Gastrointestinal AEs | 8 (8.4) | 13 (13.8) | 21 (11.1) |
| Most common AEs (≥3%) | | | |
| Anal hemorrhage | 3 (3.2) | 4 (4.3) | 7 (3.7) |
| Painful defecation | 2 (2.1) | 5 (5.3) | 7 (3.7) |
| Vomiting | 2 (2.1) | 4 (4.3) | 6 (3.2) |
| Body temperature increased | 3 (3.2) | 3 (3.2) | 6 (3.2) |
| Rectal discharge | 1 (1.1) | 3 (3.2) | 4 (2.1) |

Data are numbers of patients with percentages in parentheses.
AE = adverse event.
[a]If a patient experienced more than 1 episode of a particular AE, the patient was counted only once for the event.

patient's satisfaction with postsurgical analgesia was significantly different between treatment groups, with 89 of 94 (94.7%) patients in the DepoFoam bupivacaine group reporting "satisfied" or "extremely satisfied" responses at 72 hours after study drug administration compared with 68 of 93 (73.1%) in the placebo group ($P = .0007$).

### Safety

A total of 33 patients (17.5%) reported at least 1 treatment-emergent AE during the study, 16 (16.8%) after administration of DepoFoam bupivacaine and 17 (18.1%) after receiving placebo. The majority of AEs were mild in severity. The most frequently reported treatment-emergent AEs were anal hemorrhage and painful defecation (Table 3). No patient discontinued participation in the study due to AEs. One patient in the DepoFoam bupivacaine group experienced nail redness on day 2, which was considered by the investigator to be related to study drug. This event resolved on day 8; no other AEs reported during the study were considered related to study drug. One serious AE of mild thrombophlebitis occurred on day 5 in a patient in the placebo group. The patient was treated with anticoagulants, and the event resolved on day 6. It was not considered related to study drug by the investigator.

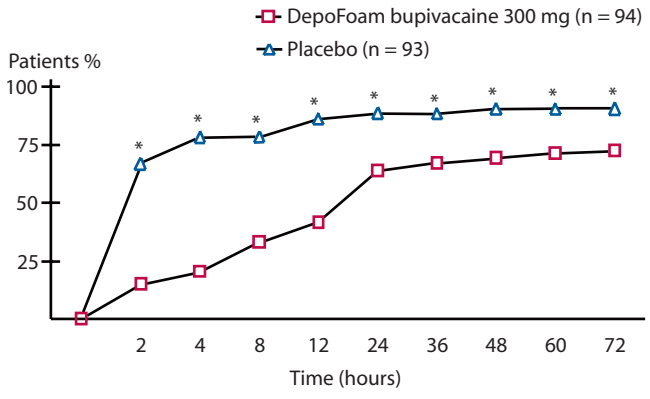


**FIGURE 5.** Time to first use of opioid rescue medication (percentage of patients) after surgery (full analysis set). *$P < .0001$.

The LS mean (SE) score on the caregiver's satisfaction with wound healing questionnaire was similar in the DepoFoam bupivacaine group (0.55 (0.12)) compared with the placebo group (0.59 (0.12)). There were no clinically meaningful changes in vital signs, hematology, or laboratory values during the course of the study.

## DISCUSSION

A single dose of DepoFoam bupivacaine 300 mg administered via a series of deep-tissue infiltrations at the close of surgery was shown effective for postsurgical pain relief in adult patients undergoing 2- or 3-column excisional hemorrhoidectomy with the use of the Milligan-Morgan technique under general anesthesia. A statistically significant reduction in cumulative pain score was shown in patients receiving DepoFoam bupivacaine compared with those receiving placebo. The efficacy of DepoFoam bupivacaine was also shown in results for other outcome measures. Significant differences in favor of DepoFoam bupivacaine were observed in the proportion of patients remaining opioid free, mean total amount of opioid rescue medications consumed, median time to first use of opioid rescue medication, BPI, and patient satisfaction with postsurgical analgesia.

The overall incidence of treatment-emergent AEs was similar in the DepoFoam bupivacaine and placebo groups. The incidence of gastrointestinal-related treatment-emergent AEs was higher in the placebo group than in the DepoFoam bupivacaine group. Because gastrointestinal side effects are well recognized sequelae of opioid treatment, this difference may be related to the increased opioid use in patients receiving placebo.

Our study involved a relatively homogeneous surgical population who were without another current painful

condition. The concomitant use of perioperative analgesic medications was also limited, so that the efficacy of DepoFoam bupivacaine could be measured without the confounding variables of other concomitant analgesics. Although we believe that this well-controlled study design facilitated monitoring of treatment-related efficacy and safety signals associated with DepoFoam bupivacaine in this surgical setting, caution is warranted when interpreting results. In this study, DepoFoam bupivacaine was administered locally via wound infiltration without an active comparator. Results from an active-controlled, multimodal study of DepoFoam bupivacaine compared with bupivacaine HCl, reflecting the current standard of use in the setting of hemorrhoidectomy, are pending publication. The results of the current study cannot be extrapolated to scenarios where other methods of administration are used (eg, nerve block, epidural administration) or to broader patient populations such as those on chronic opioid therapy or taking other concomitant medications. Results from randomized studies of DepoFoam bupivacaine in other surgical models revealed similar results and are pending publication. Assessments of pain and satisfaction are subjective, an inherent limitation of all pain studies. Nevertheless, our study showed that DepoFoam bupivacaine is a potentially useful therapeutic option for pain management after hemorrhoidectomy procedures. Patient satisfaction was increased. The use of DepoFoam bupivacaine in this setting was associated with statistically significantly lower pain scores and decreased opioid requirements in the acute postsurgical period. Reduction in opioid consumption may result in fewer opioid-related AEs, faster ambulation, and shorter duration of postsurgical hospital stays.

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