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Liposomal Bupivacaine in Implant-Based Breast Reconstruction

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Purpose: This study evaluates the role of liposomal bupivacaine in implant-based breast reconstruction.

Methods: A prospective, randomized, single-blind trial of liposomal bupivacaine in implant-based breast reconstruction was performed. Patients in the control arm were treated with 20 mL 0.25% bupivacaine with epinephrine 1:200,000 to each breast pocket. Patients in the experimental arm were treated with 10 mL 1.3% liposomal bupivacaine delivered to each breast pocket. Pain scores were recorded over the course of patients' hospital stay. Consumption of pain medications, benzodiazepines, and anti-emetics was monitored. Length of stay and other direct cost data were collected.

Results: Twenty-four patients were enrolled, with 12 women randomized to each arm. Average postoperative pain scores were 3.66 for patients in the control arm and 3.68 for patients in the experimental arm. Opioid consumption was 1.43 morphine equivalent dosing/h for patients in the control arm and 0.76 morphine equivalent dosing/h for patients in the experimental arm ($P = 0.017$). Diazepam consumption was 0.348 mg/h for patients in the control arm and 0.176 mg/h for patients in the experimental arm ($P = 0.011$). Average length of hospital stay was 46.7 hours for patients in the control arm and 29.8 hours for patients in the experimental arm ($P = 0.035$). Average hospital charges were $18,632 for patients in the control arm and $10,828 for patients in the experimental arm ($P = 0.039$).

Conclusions: Liposomal bupivacaine reduces opioid and benzodiazepine consumption, length of stay, and hospital charges. These data support a role for liposomal bupivacaine in implant-based breast reconstruction. *(Plast Reconstr Surg Glob Open 2017;5:e1559; doi: 10.1097/GOX.0000000000001559; Published online 20 November 2017.)*

INTRODUCTION

Breast reconstruction is one of the most commonly performed reconstructive procedures in the United States. In 2016 alone, 109,256 breast reconstruction procedures were performed.[1] The management of acute and chronic postoperative pain following mastectomy and breast reconstruction is a challenging problem. Postoperative pain is a major factor contributing to delayed mobilization and prolonged hospital stay in the acute period following breast reconstruction.[2] According to 1 study, as many as 50% of women undergoing mastectomy and breast reconstruction will develop postoperative pain syndromes.[3] Other studies have demonstrated a higher incidence of chronic pain in women undergoing implant-based breast reconstruction compared with women undergoing mastectomy alone or breast reconstruction without an implant.[4] Improved pain control following implant-based breast reconstruction may be associated with reduced morbidity, decreased length of hospital stay (LOS), and improved patient satisfaction. These improved patient outcomes may have a significant impact on hospitals, providers, and patients. In this age of cost containment and efficient care models, improving our patients' care experience is beneficial to all parts of the health care equation.

Researchers have studied a variety of treatment modalities in an attempt to achieve improved postoperative pain

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Received for publication September 6, 2017; accepted September 15, 2017.

This project was registered with ClinicalTrials.gov, Protocol ID # 5150012.

Presented at the Plastic Surgery The Meeting 2016, Los Angeles, Calif.

DOI: 10.1097/GOX.0000000000001559

Disclosure: *Supported, in part, by a Pilot Research Grant from the Plastic Surgery Foundation (PRG 350440). The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors using funding from a Pilot Research Grant from the Plastic Surgery Foundation.*

control following breast reconstruction. Several studies published in the last decade have evaluated the role of local anesthetics administered via continuous infusion pump systems. Patients receiving postoperative anesthesia via continuous infusion pump systems used less patient-controlled analgesics and transitioned earlier to oral narcotics.[5] However, these pump systems are cumbersome for patients, can be costly, and can be associated with complications such as infection and pump malfunction. Other fairly recent studies have examined the role of a postoperative transversus abdominis plane block using a catheter placed under ultrasound guidance following microsurgical breast reconstruction. These studies demonstrated a shorter length of stay, decreased patient controlled analgesia usage, and fewer episodes of nausea and vomiting.[6] However, placing these catheters requires an additional procedure that presents additional costs and is associated with complications such as migration, intravascular placement, and infection. It also requires some specialized expertise not universally available. Because of the challenges presented with these modalities, the mainstay of postoperative pain management continues to be opioids, which are administered via the oral or intravenous route. However, these medications have serious problems of their own. Complications such as nausea, vomiting, constipation, pruritus, sedation, respiratory-depression, tolerance, drug-dependence, and opioid-induced hyperalgesia have been well described. The multitude of side effects associated with these medications has renewed interest in alternative methods to achieve and improve postoperative pain control.

One such method utilizes an innovative vehicle for targeted and prolonged drug delivery—the liposome. A liposome is a spherical, phospholipid bilayer construct that dissolves water soluble compounds.[7] This unique structure of liposomes allows them to dissolve agents, improve their stability, and deliver them over a longer duration of time.[8] Liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, Parsippany, N.J.) is a liposomal formulation of a commonly used anesthetic agent (bupivacaine) that shows significant promise as part of a multimodal approach to postoperative pain control. This agent provides up to 72 hours of postoperative pain relief with a single injection so that the placement of a catheter is not required.[8] Studies have evaluated the role of this agent in total knee arthroplasty, inguinal hernia repair, hemorrhoidectomy, bunionectomy, and breast augmentation and have demonstrated lower pain scores, lower opioid consumption, and fewer opioid-related adverse events.[9] More recently, retrospective studies have evaluated a role for liposomal bupivacaine in implant-based breast reconstruction with promising findings.[10,11] However, at a cost of roughly $300 for a 20 mL vial, reservations remain regarding the costs associated with this drug, and to date, the role of liposomal bupivacaine has not been evaluated in prospective, randomized, controlled studies in the setting of tissue-expander and implant-based breast reconstruction.

The development and validation of an enhanced protocol for postoperative pain management in patients undergoing breast reconstruction has important implications. Perhaps most significantly, improved postoperative pain management has the potential to reduce the length of patients' hospital stays and early postoperative morbidity, leading to significant savings in health care costs. Decreased opioid use in the perioperative period also reduces the risk of associated side effects such as nausea, vomiting, drug-dependence, and opioid-induced hyperalgesia. Better pain control may contribute to improved patient satisfaction, reduced chronic postsurgical pain, and improved long-term patient-reported outcomes. In such, the authors set out to perform the first prospective clinical study of liposomal bupivacaine in the context of implant-based breast reconstruction. We hypothesized that this agent may contribute to reduced pain scores, reduced opioid and benzodiazepine consumption, decreased length of stay, and reduced health care costs.

METHODS

This project was funded in part by a Pilot Research Grant from the Plastic Surgery Foundation (PRG 350440). The study was performed with approval of our institutional review board (no. 5150012). Patients were recruited for participation in this study during their preoperative consultation for breast reconstruction. Inclusion criteria were any women over the age of 18 years of age undergoing immediate unilateral or bilateral tissue-expander or direct-to-implant breast reconstruction following skin-sparing or nipple-sparing mastectomy. Exclusion criteria included women with a history of hypersensitivity reactions to local anesthetic agents; women with a history of chronic pain such as fibromyalgia, chronic migraine headaches, or psychiatric disorders other than depression or anxiety; women undergoing breast reconstruction with a latissimus dorsi muscle flap in addition to a tissue expander or implant; women with a history of prior breast augmentation; and women with a history of impaired hepatic function.

Basic demographic information was recorded for all patients including age, body mass index, and smoking status. Patients were randomized to 1 of 2 study groups using a computer randomizer. Patients in the control group (bupivacaine) were treated intraoperatively with injections of 0.25% bupivacaine and epinephrine 1:200,000, with 20 mL (50 mg) delivered to perform a field block of each breast pocket. Patients in the control group (liposomal bupivacaine) were treated intraoperatively with injections of 1.33% liposomal bupivacaine, with 10 mL (133 mg) delivered to perform a field block of each breast pocket.

Intraoperatively, each breast pocket was infiltrated to perform a field block as described by Buitelaar et al.[12] including:

- Intramuscular infiltration of the pectoralis major along the caudal border of the clavicle, targeting the supraclavicular nerves
- Along the ipsilateral parasternal line, targeting the anterior cutaneous branches of the first to sixth intercostal nerves
- Along a line 1 cm posterior and parallel to the anterior axillary line, extending under the pectoralis major muscle in the axilla, targeting the lateral cutaneous branches of the second to seventh intercostal nerves[12]

Additional anesthetic was infiltrated along the base of the patients' mastectomy flaps and in any areas where deep sutures had been placed to anchor acellular dermal matrix along the chest wall and along the pectoralis major muscle.[13]

Postoperatively, all patients were admitted and received standard pain management per our department's standard protocol with hydrocodone/acetaminophen 5 mg/325 mg every 4 hours as needed for moderate pain, hydrocodone/acetaminophen 10 mg/325 mg every 4 hours as needed for severe pain, and hydromorphone 0.2 mg intravenously every 2 hours as needed for breakthrough pain. Patients received diazepam 5 mg every 6 hours around the clock for muscle spasms. Patients received ondansetron 4 mg IV every 6 hours as needed for nausea and vomiting. Our standardized postoperative protocol for the management of pain, nausea, and muscle spasms is summarized in Table 1.

Postoperatively, we assessed pain levels, opioid consumption, benzodiazepine consumption, opioid-related adverse events, length of stay, and hospital charges for length of stay. Postoperative pain levels were determined with a numeric rating scale, where patients were asked to rate pain from 0–10, where 0 = no pain, 10 = worst possible pain. Pain levels were determined on postoperative day 0 (upon waking in the postanesthesia care unit), then every 4 hours postoperatively, over the course of patients' stay in the hospital. Postoperative opioid consumption was determined in each group while inpatient, beginning when patients arrived in the postanesthesia care unit. Opioid consumption was recorded and converted to morphine equivalent dosing (MED) per hour of hospital stay to simplify and standardize comparisons. Benzodiazepine consumption, in milligrams of diazepam, was recorded for all patients. Opioid-related adverse events, specifically, nausea or vomiting were recorded. Patients were also monitored for any other adverse events in the postoperative period. Antiemetic consumption, in milligrams of ondansetron, and rates of postoperative nausea and vomiting were recorded for all patients. LOS was recorded by recording the difference between the time the postoperative admission order was placed and the time the postoperative discharge order was placed. Hospital charges beyond the operating room costs were calculated and recorded based on length of stay, whereby the charge for a 1 midnight stay at a basic level of care was $9721. The additional cost of liposomal bupivacaine $297 was also included for hospital costs for patients in our experimental group.

Basic statistical analyses were performed and consisted of pain scores, opioid consumption, benzodiazepine consumption, antiemetic consumption, LOS, and hospital charges. Statistical significance was ascertained with a paired, 2-tailed Student's t test, with statistical significance designated for $P < 0.05$.

Table 1. Standardized Postoperative Protocol for Pain Control following Implant-Based Breast Reconstruction

Moderate pain	Hydrocodone/acetaminophen 5 mg/325 mg Q4H PRN
Severe pain	Hydrocodone/acetaminophen 10 mg/325 mg Q4H PRN
Breakthrough pain	Hydromorphone 0.2 mg IV Q2H PRN
Muscle spasms	Diazepam 5 mg PO Q6H around the clock
Nausea and vomiting	Ondansetron 4 mg IV Q6H PRN

RESULTS

Between September 2015 and September 2016, 24 patients were enrolled in this study. A per protocol planned interim analysis was performed at $n = 24$ patients and study enrollment ended when significance was reached for all major outcome measures. Average age (56.2 in the bupivacaine group versus 48.7 in the liposomal bupivacaine group; $P = 0.16$) and BMI (25.3 in the bupivacaine group versus 26.0 in the liposomal bupivacaine group; $P = 0.69$) was similar in both groups. There was no significant difference in average fill (273.8 CCs in the bupivacaine group versus 351.9 CCs in the liposomal bupivacaine group; $P = 0.31$) in either group. There was 1 delayed reconstruction in the bupivacaine group and 2 delayed reconstructions in the liposomal bupivacaine group. There were no smokers in the bupivacaine group and 1 smoker in the liposomal bupivacaine group. Acellular dermal matrices were used in all but 1 patient in the bupivacaine group and all but 4 patients in the liposomal bupivacaine group. There were 2 unilateral procedures in the bupivacaine group, and 3 unilateral procedures in the liposomal bupivacaine group. Demographic data are summarized in Tables 2, 3.

There was no significant difference in average pain scores over the first 24 hours postoperatively (3.66 in the bupivacaine group versus 3.68 in the liposomal bupivacaine group; Fig. 1). Postoperative opioid consumption was significantly lower in the liposomal bupivacaine group (0.76 MED/h versus 1.43 MED/h; $P = 0.017$; Fig. 2). Benzodiazepine consumption was significantly lower in the liposomal bupivacaine group (0.18 mg diazepam/h versus 0.35 mg diazepam/h; $P = 0.011$; Fig. 3). There was no significant difference in rates of nausea and vomiting (3 in the bupivacaine group versus 2 in the liposomal bupivacaine group) or antiemetic consumption (7.33 mg in the bupivacaine group versus 5.75 mg in the liposomal bupivacaine group; $P = 0.51$; Fig. 4). Length of stay was significantly shorter in the liposomal bupivacaine group (29.8 hours in the liposomal bupivacaine group versus 46.7 hours in the bupivacaine group; $P = 0.035$; Fig. 5). Hospital charges were significantly lower in the liposomal bupivacaine group ($10,828 versus $18,632; $P = 0.039$; Fig. 6). There were no significant adverse events in either group.

DISCUSSION

Breast cancer continues to be the most common cancer afflicting women in the United States. Approximately 12% of women will suffer from invasive breast cancer over the course of their lives. In 2017 alone, over 250,000 women will be diagnosed with invasive breast cancer and another 60,000 with noninvasive breast cancer.[14] An increasing number of women are now pursuing breast reconstruction following mastectomy. According to one study, 46% of women underwent breast reconstruction following bilateral mastectomies in 1998 compared with 63% of women in 2007.[15]

Table 2. Demographic Data for Patients Enrolled in Liposomal Bupivacaine and Bupivacaine Groups

Demographics							
Group	**BMI (kg/m²)**	**Laterality**	**Average Fill (CCs)**	**Laterality**	**Timing**	**ADM**	**Smoker**
Bupivacaine	25.6	Unilateral	300	Unilateral	Immediate	Yes	No
Bupivacaine	20.94	Bilateral	500	Bilateral	Immediate	Yes	No
Bupivacaine	21.36	Bilateral	150	Bilateral	Immediate	Yes	No
Bupivacaine	24.8	Bilateral	250	Bilateral	Immediate	Yes	No
Bupivacaine	27.81	Bilateral	375	Bilateral	Immediate	Yes	No
Bupivacaine	32.54	Bilateral	150	Bilateral	Immediate	Yes	No
Bupivacaine	21.56	Bilateral	300	Bilateral	Immediate	Yes	No
Bupivacaine	32.47	Bilateral	100	Bilateral	Delayed	No	No
Bupivacaine	20.18	Unilateral	300	Unilateral	Immediate	Yes	No
Bupivacaine	22.11	Bilateral	210	Bilateral	Immediate	Yes	No
Bupivacaine	24.27	Bilateral	450	Bilateral	Immediate	Yes	No
Bupivacaine	30.4	Bilateral	200	Bilateral	Immediate	Yes	No
Average	25.33666667		273.75				
Liposomal bupivacaine	22.13	Bilateral	650	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	26.53	Bilateral	262.5	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	32.1	Bilateral	800	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	24.58	Bilateral	400	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	24.17	Unilateral	350	Unilateral	Immediate	Yes	No
Liposomal bupivacaine	24.96	Bilateral	100	Bilateral	Delayed	No	No
Liposomal bupivacaine	29.01	Bilateral	450	Bilateral	Immediate	No	No
Liposomal bupivacaine	29.98	Bilateral	150	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	22.19	Bilateral	535	Bilateral	Immediate	Yes	No
Liposomal bupivacaine	27.98	Unilateral	300	Unilateral	Immediate	Yes	Yes
Liposomal bupivacaine	23.78	Bilateral	125	Bilateral	Immediate	No	No
Liposomal bupivacaine	24.21	Unilateral	100	Unilateral	Delayed	No	No
Average	25.96833333		351.875				

ADM, acellular dermal matrix.

Postoperative pain management remains a challenging—and important—problem following mastectomy and reconstruction. Nissen et al.[16] noted that factors that may contribute to a poor quality of life following breast reconstruction include increased length of hospitalization and postoperative pain. These findings are especially relevant for women undergoing implant-based breast reconstruction, who may suffer from greater pain postoperatively than women undergoing reconstruction without an implant.[17] As discussed previously, as many as 50% of women will develop postoperative pain syndromes following mastectomy and reconstruction. Severe, poorly controlled postoperative pain has been consistently associated with the development of chronic pain syndromes.[18] This in turn can detrimentally affect patients' quality of life.

Table 3. Average Demographic Data for Patients with Statistical Analysis

	Bupivacaine Group (N = 12)	**Liposomal Bupivacaine Group (N = 12)**	***P***
Age (y)	56.2±12.6	48.7±12.5	0.16
BMI	25.3±4.5	25.9±3.2	0.69
Laterality			
Unilateral	2 (16.7)	3 (25.0)	1
Bilateral	10 (83.3)	9 (75.0)	
Average fill	273.8±122.6	351.9±226.6	0.31
Intraoperative fill			
Timing			
Immediate	11 (91.7)	10 (83.3)	1
Delayed	1 (8.3)	2 (16.7)	
ADM			
Yes	11 (91.7)	8 (66.7)	0.32
No	1 (8.3)	4 (33.3)	
Smoker			
Yes	0	1 (8.3)	1
No	12 (100.0)	11 (91.7)	

These data have renewed interest in strategies to manage postoperative pain. Local anesthetic agents offer a simple and highly effective intraoperative intervention that may reduce postoperative pain. These agents block voltage-gated sodium channels, inhibiting neuronal depolarization and transmission of pain signals. However, until recently, a significant downside of these drugs has been their relatively short duration of action. The unique liposomal formulation of bupivacaine allows for a more sustained release that provides up to 72 hours of analgesia. Although this drug was approved by the Food and Drug Administration in 2011, data supporting the use of this drug in implant-based breast reconstruction remain limited.

Our study demonstrates that patients undergoing implant-based breast reconstruction who received an intraoperative field block with liposomal bupivacaine consumed less opioid pain medications and less benzodiazepine medications compared with patients who had received a field block with bupivacaine with epinephrine (Table 4). Length of stay and the resulting hospital costs were significantly lower in this group of patients as well. There was no significant difference in pain scores, rates of nausea and vomiting, and antiemetic consumption. The findings of this study represent the best evidence to date supporting a role for liposomal bupivacaine in implant-based breast reconstruction.

Although pain scores were similar in both groups of patients, it is noteworthy that these pain scores were achieved with significantly lower opioid requirements in the liposomal bupivacaine group. This represents an important finding, as opioid medications are associated with a multitude of undesirable side effects. Benzodiazepine medications were also consumed at a significantly lower rate in patients in our experimental group. These medications are administered for muscle spasms and are ordered around the clock

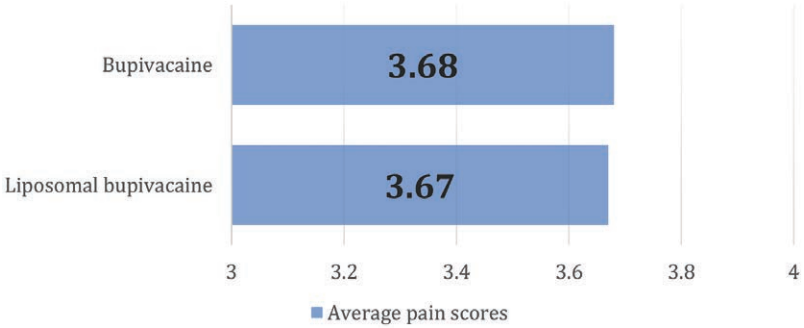

Fig. 1. Average pain scores in liposomal bupivacaine and bupivacaine groups after 24 hours.

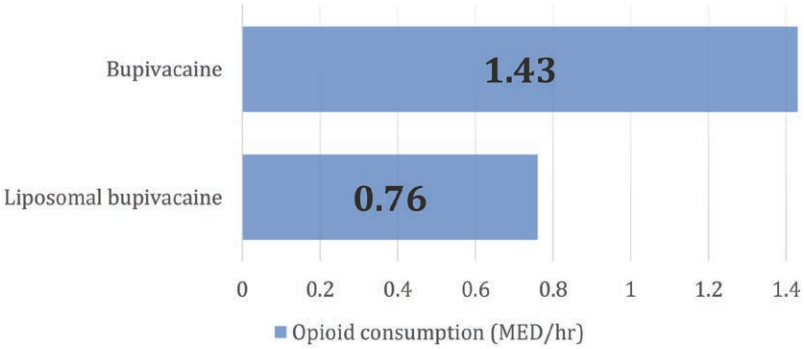

Fig. 2. Opioid consumption in MED/h in liposomal bupivacaine and bupivacaine groups for course of hospital stay.

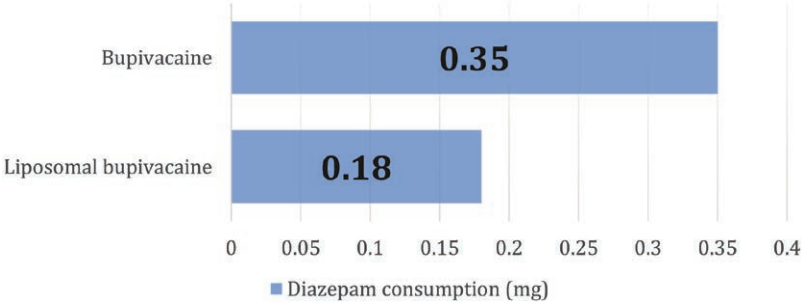

Fig. 3. Benzodiazepine consumption in mg/h in liposomal bupivacaine and bupivacaine groups for course of hospital stay.

for patients undergoing breast reconstruction at our institution. Interestingly, we noted that patients in our liposomal bupivacaine group refused this medication after receiving their first or second dose. This in turn contributed to the significantly lower rate of consumption of benzodiazepines. These medications are associated with significant side effects of their own, including sedation, respiratory depression, and delirium, which are particularly concerning in older patients undergoing breast reconstruction. The Food and Drug Administration now requires boxed warnings on opioids and benzodiazepines to warn patients of the significant risks associated with combining these medications.[19]

In theory, reduced opioid consumption should contribute to reduced opioid-related adverse events such as nausea and vomiting and reduced antiemetic consumption. This effect was not observed in our study, as rates of antiemetic consumption and postoperative nausea and vomiting were similar in both groups of patients. However, other studies evaluating liposomal bupivacaine in other contexts have noted a lower rate of opioid-related adverse events.[9]

Perhaps, our most significant finding was a significantly lower LOS (by 16.9 hours; $P = 0.035$) and significantly lower hospital costs (by $7,804; $P = 0.039$) for patients receiving liposomal bupivacaine following breast reconstruction. The majority of patients receiving liposomal bupivacaine were discharged on the day of surgery or on postoperative day 1 (10 of 12 patients). In contrast, the majority of patients receiving bupivacaine (7 of 12 patients) were discharged on postoperative day 2 or later. This find-

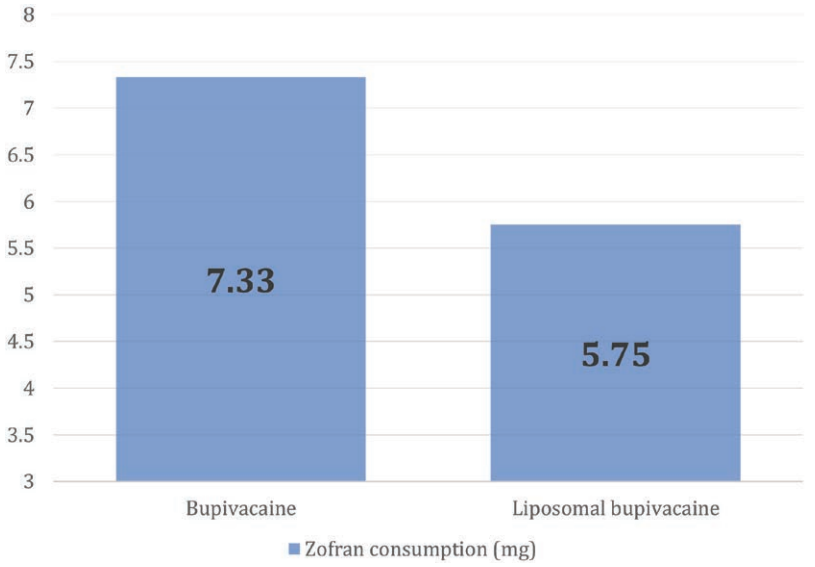

Fig. 4. Rates of ondansetron consumption for liposomal bupivacaine and bupivacaine groups.

Fig. 5. LOS for liposomal bupivacaine and bupivacaine groups.

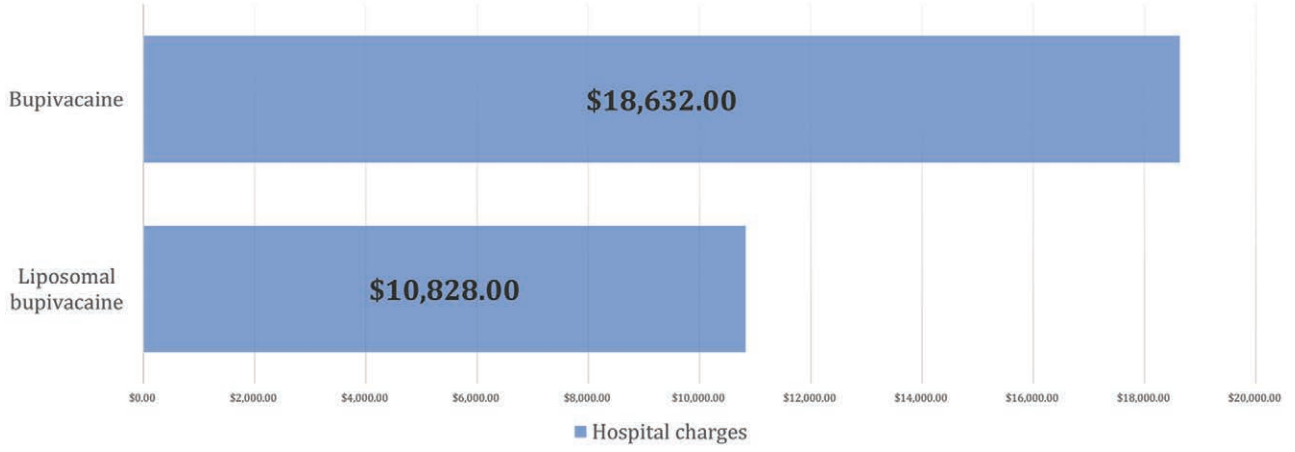

Fig. 6. Hospital charges for liposomal bupivacaine and bupivacaine groups.

ing has important implications in today's health care environment, with increasing pressure on providers to lower costs while improving patient outcomes. Increased postoperative pain and length of stay following breast reconstruction have been previously associated with reduced quality of life following reconstruction. Both of these variables were significantly reduced in patients in our study who received liposomal bupivacaine following breast reconstruction. Improved outcomes and patient satisfaction may contribute to improved scores on the Hospital Con-

Table 4. Summary of Collected Data

Group	Liposomal Bupivacaine Group	Bupivacaine	*P*
Pain score	3.66	3.68	> 0.05
Nausea and vomiting (pts)	3	2	> 0.05
Opioid consumption	0.76 MED/h	1.43 MED/h	0.017
Benzodiazepine consumption	0.18 mg diazepam/h	0.35 mg diazepam/h	0.011
Antiemetic consumption (mg)	7.33	5.75	> 0.05
Length of stay (h)	29.8	46.7	0.035
Hospital charges	$10,828	$18,632	0.039

sumer Assessment of Healthcare Providers and Systems, a survey instrument required by the Centers for Medicare and Medicaid Services for hospitals in the United States. Hospital Consumer Assessment of Healthcare Providers and Systems scores are now directly linked to hospital reimbursements, making scores on this assessment a significant priority for hospitals and providers across the nation.

A limitation of this study was our fairly small sample size of 24 patients. Although our study achieved significance for all major outcome measures, larger, prospective studies will be better powered to tease out the differences between liposomal bupivacaine and other means of postoperative pain control. In addition, our study was single blinded, which may have introduced bias to our study. It would be difficult, if not impossible, to perform a double-blind study comparing liposomal bupivacaine to standard formulations of bupivacaine. Liposomal bupivacaine is a milky, white solution, whereas bupivacaine is clear. For this reason, we chose not to attempt double blinding for our study.

CONCLUSIONS

Patients undergoing implant-based breast reconstruction who received liposomal bupivacaine consumed less opioid and benzodiazepine medications and had a lower length of stay and lower hospital costs compared with patients receiving bupivacaine with epinephrine. This provides convincing data supporting the use of liposomal bupivacaine use as part of a multimodal pain management strategy following implant-based breast reconstruction.

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