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Liposomal Bupivacaine Analgesia in Deep Inferior Epigastric Perforator Flap Breast Reconstruction: A Retrospective Cohort Study

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Background: Liposomal bupivacaine (LB) can be used for postsurgical analgesia after breast reconstruction. We examined real-world clinical and economic benefits of LB versus bupivacaine after deep inferior epigastric perforator (DIEP) flap breast reconstruction.

Methods: This retrospective cohort study used the IQVIA claims databases to identify patients undergoing primary DIEP flap breast reconstruction in 2016–2019. Patients receiving LB and those receiving bupivacaine were compared to assess opioid utilization in morphine milligram equivalents (MMEs) and healthcare resource utilization during perioperative (2 weeks before surgery to 2 weeks after discharge) and 6-month postdischarge periods. A generalized linear mixed-effects model and inverse probability of treatment weighting method were performed.

Results: Weighted baseline characteristics were similar between cohorts (LB, n = 669; bupivacaine, n = 348). The LB cohort received significantly fewer mean MMEs versus the bupivacaine cohort during the perioperative (395 versus 512 MMEs; rate ratio [RR], 0.771 [95% confidence interval (CI), 0.677–0.879]; P = 0.0001), 72 hours after surgery (63 versus 140 MMEs; RR, 0.449 [95% CI, 0.347–0.581]; $P < 0.0001$), and inpatient (154 versus 303 MMEs; RR, 0.508 [95% CI, 0.411–0.629]; $P < 0.0001$) periods; postdischarge filled opioid prescriptions were comparable. The LB cohort was less likely to have all-cause inpatient readmission (odds ratio, 0.670 [95% CI, 0.452–0.993]; $P = 0.046$) and outpatient clinic/office visits (odds ratio, 0.885 [95% CI, 0.785–0.999]; $P = 0.048$) 3 months after discharge than the bupivacaine cohort; other all-cause healthcare resource utilization outcomes were not different.

Conclusions: LB was associated with fewer perioperative MMEs and all-cause 3-month inpatient readmissions and outpatient clinic/office visits than bupivacaine in patients undergoing DIEP flap breast reconstruction. *(Plast Reconstr Surg Glob Open 2024; 12:e5874; doi: 10.1097/GOX.0000000000005874; Published online 7 June 2024.)*

INTRODUCTION

Deep inferior epigastric perforator (DIEP) flap breast reconstruction is the most common nonimplant breast reconstruction procedure, accounting for 17% of all such procedures in 2020.[1,2] DIEP flap breast reconstruction preserves underlying muscle and may lead to higher overall patient satisfaction than implant-based reconstruction.[3,4] However, patients undergoing DIEP flap breast reconstruction can experience considerable postoperative pain that may become persistent.[5,6] Postoperative breakthrough pain is often managed with opioids, which can be associated with respiratory depression, vomiting, nausea, constipation, dizziness, and drowsiness.[7–10] Additionally, postdischarge opioid prescriptions could contribute to subsequent opioid use disorder,[11] and postsurgical opioid use among opioid-naive patients undergoing breast reconstruction can be associated with long-term opioid use.[12] Therefore, strategies to effectively manage pain after breast reconstruction while minimizing opioid use are needed.

Enhanced recovery pathways (ERPs; eg, enhanced recovery after surgery protocols) are associated with

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lower postoperative pain, shorter length of stay, and fewer opioid-related adverse effects.[13–16] Regional pain blocks [eg, transversus abdominis plane (TAP) blocks, paravertebral blocks, erector spinae plane blocks] may be included in ERP protocols for breast reconstruction as a component of multimodal management.[17–19] In a systematic review of 28 studies examining pain management for breast reconstruction, opioid consumption was reduced in all seven studies that included ERP protocols and in eight of nine studies that included TAP or paravertebral blocks.[20] In this systematic review, liposomal bupivacaine, a formulation of the local anesthetic bupivacaine enabling controlled release of bupivacaine for prolonged analgesia, was highlighted for pain management after breast reconstruction.[20] Previous studies investigated liposomal bupivacaine administered as a TAP block (including as part of an ERP protocol) for DIEP flap breast reconstruction,[15–17,21–23] with some showing reduced opioid consumption versus historical controls.[15,23] Prior studies of DIEP flap procedures found that liposomal bupivacaine was associated with lower opioid use compared with bupivacaine administered via TAP blocks.[22] However, not all studies examining liposomal bupivacaine demonstrated reduced opioid consumption or pain scores compared with controls, suggesting additional data are needed.[24] For example, no difference in opioid consumption or pain scores was observed in a randomized controlled trial comparing liposomal bupivacaine via TAP block with an ERP protocol using bupivacaine hydrochloride via TAP block.[25] Another recent double-blind randomized controlled trial that compared TAP blocks with liposomal bupivacaine versus plain bupivacaine (as a component of an enhanced recovery after surgery protocol) for DIEP flap breast reconstruction found no significant differences between treatment groups in daily opioid consumption or pain scores through 1 week after surgery.[26]

Select studies have assessed additional outcomes with liposomal bupivacaine versus comparators, including length of stay and healthcare resource utilization measures (eg, costs). Liposomal bupivacaine (LB) was associated with reduced length of stay, costs, and 30-day readmission rates in prior analyses combining abdominal and breast reconstruction procedures.[27] Some, but not all, previous studies reported significantly shorter length of stay for patients receiving liposomal bupivacaine via a TAP block for DIEP flap reconstruction specifically.[15,16,21–23] Other studies assessing costs with liposomal bupivacaine via TAP block versus comparators in DIEP flap reconstruction have not observed substantial cost differences between groups.[21,22]

Although previous breast reconstruction studies reported reduction in inpatient opioid consumption with liposomal bupivacaine, some showed no evidence of significant reduction, and how liposomal bupivacaine affected other outcomes (including postdischarge outcomes) after DIEP flap procedures is less clear. Accordingly, this retrospective study assesses (1) opioid intake in morphine milligram equivalents (MMEs) during the hospital stay and after discharge, and (2) hospital length of stay and postdischarge healthcare resource utilization among patients who received liposomal bupivacaine versus bupivacaine following DIEP flap breast reconstruction surgery.

Takeaways

Question: How does the use of liposomal bupivacaine (LB) versus bupivacaine for deep inferior epigastric perforator flap breast reconstruction affect opioid consumption and healthcare resource utilization in real-world settings?

Findings: This retrospective cohort study using a claims database found that patients who received LB required fewer opioids in the perioperative period (2 weeks before and after surgery) and had fewer inpatient readmissions and outpatient visits in the 3 months after discharge than patients who received bupivacaine.

Meaning: This analysis of real-world data suggests that incorporating LB into a multifaceted pain management protocol for deep inferior epigastric perforator flap breast reconstruction may reduce opioid consumption and healthcare resource utilization.

METHODS

Study Design

This retrospective cohort analysis used the IQVIA linkage claims databases, which include data from the Charge Data Master in both inpatient and outpatient settings, pharmacy prescription claims, and outpatient medical claims IQVIA databases.[28] Because patient records are deidentified, this analysis was exempt from institutional review board review and informed consent requirements per US Department of Health and Human Services policy (Title 45 Code of Federal Regulations, Part 46 of the United States). We analyzed records of patients undergoing inpatient DIEP flap breast reconstruction from 2016 to 2019.

Inclusion criteria for this study were patients aged 18 years or older undergoing a primary open DIEP procedure (defined by International Classification of Diseases, 10th Revision procedure codes 0HRT077, 0HRU077, 0HRV077) who received either liposomal bupivacaine or bupivacaine with 6 months or more continuous enrollment before and after surgery. Prior opioid exposure (opioid naive or opioid experienced) for subgroup analyses was defined by any filled opioid prescriptions in the 6 months before surgery. To remove extreme outcome values for continuous variables, patients with length of stay or opioid use (in total MMEs; perioperative and follow-up) values greater than 95th percentile of the respective distribution were excluded.

Study Outcomes

Clinical and healthcare resource utilization outcomes were compared between the liposomal bupivacaine and bupivacaine cohorts during the perioperative period (2 weeks before surgery to 2 weeks after discharge), the inpatient period (entire hospital stay), and the up-to-6-month postdischarge period, including the continued (> 2 weeks to 3 months after discharge) and persistent

(4–6 months after discharge) periods. Clinical outcomes included opioid intake and use of nonopioid pain medication during the perioperative period, filled opioid prescriptions in the continued and persistent periods (measured in MMEs), and inpatient opioid-related adverse events. Subgroup analyses comparing opioid consumption between the liposomal bupivacaine and bupivacaine cohorts were performed according to prior opioid exposure status and unilateral and bilateral surgery subgroups. Inpatient and up-to-3-month postdischarge healthcare resource utilization outcomes included inpatient length of stay, measured from the hospital admission date to discharge date. Inpatient readmissions, emergency department visits, and outpatient clinic/office visits were defined by the data field "place of service codes," indicating the location of healthcare service,[29] and were analyzed according to all causes and pain-related causes.

Statistical Analysis

A generalized linear mixed-effects model was used to compare outcomes. In addition, an inverse probability of treatment weighting method, which weighs characteristics by the inverse propensity score, was used [liposomal bupivacaine: 1/(propensity score]; non–liposomal bupivacaine: 1/[1– propensity score]).[30–32] A propensity score was obtained by regressing treatment (ie, liposomal bupivacaine) probability against age, Quan-Charlson Comorbidity Index, prior opioid exposure, history of cancer, history of metastatic cancer, insurance type, surgical year, breast laterality, teaching hospital status, and hospital region. Binary outcomes (eg, admissions, emergency department visits, outpatient clinic visits) were analyzed with a binary distribution and a log or cloglog link function. Opioid use outcomes (ie, opioid intake in MMEs during the perioperative periods and filled opioid prescriptions) were analyzed with a Tweedie distribution and a log link function. Length of stay (LOS) was analyzed with a negative binomial distribution with a log link function. All statistical analyses were performed using SAS, version 9.4 or later (SAS Institute; Cary, N.C.).

RESULTS

Patient and Hospital Characteristics

In total, 1017 female patients met the inclusion criteria (Fig. 1). The weighted distribution of baseline patient and hospital characteristics was comparable between the liposomal bupivacaine and bupivacaine cohorts, with standardized differences across all variables less than 20%. Each cohort had approximately the same percentage of opioid-naive participants (~57%), mean age (~51 years), and Quan-Charlson Comorbidity Index (liposomal bupivacaine cohort: 2.66; bupivacaine cohort: 2.50) after weighting. Most patients had history of nonmetastatic cancer and underwent bilateral surgery. Most of the procedures were performed at urban hospitals in the United States (Table 1).

Clinical Outcomes

During the perioperative period, opioid intake for the liposomal bupivacaine cohort was significantly lower than the bupivacaine cohort (mean MMEs, 395 versus 512; $P = 0.0001$) (Fig. 2). Opioid intake was ~50% lower compared with the bupivacaine cohort 72 hours after surgery (mean MMEs, 63 versus 140; $P < 0.0001$) and during the entire inpatient period (mean MMEs, 154 versus 303; $P < 0.0001$). Notably, the proportion of patients using most nonopioid medications was similar between the bupivacaine and liposomal bupivacaine cohorts (11.5% and 10.6%, respectively for COX2-inhibitors; 27.3% and 32.3%, respectively, for gabapentin; 22.1% and 17.2%, respectively, for ketamine; and 36.2% and 42.3%, respectively, for nonsteroidal antiinflammatory drugs; $P \geq 0.06$ for all). The bupivacaine cohort received more acetaminophen versus the liposomal bupivacaine cohort (84% versus 75%, $P < 0.01$); however, additional adjustment for acetaminophen in the regression model suggested that opioid use in the perioperative period was unchanged (data not shown).

Filled opioid prescriptions were similar between cohorts during the postdischarge period [$P = 0.715$ (continued period: $P = 0.551$; persistent period: $P = 0.237$)]. There were no inpatient opioid-related adverse events identified. During the 6 months after discharge, there was no instance of opioid use disorder.

Similar results of perioperative opioid intake were observed by subgroup analysis according to opioid exposure and laterality. Specifically, the lower opioid intake in the liposomal bupivacaine cohort was more pronounced in the opioid-experienced and bilateral subgroups (Tables 2 and 3, respectively). Filled opioid prescriptions during the postdischarge period (continued and persistent periods) were mostly nonsignificantly different between cohorts regardless of prior opioid exposure and laterality. Subgroup analysis revealed somewhat higher filled prescriptions in the liposomal bupivacaine cohort opioid-naive subgroup during the continued period versus the bupivacaine cohort (37 versus 20; $P = 0.020$), and among the bilateral subgroup during the persistent period (102 versus 70; $P = 0.0086$), although the sample size was relatively small.

Only 11 patients (1%) included in the analysis had received immediate DIEP procedures. Additional analysis excluding these patients did not materially change the results (data not shown).

LOS and All-cause/Pain-related Healthcare Resource Utilization Outcomes

LOS was similar between the liposomal bupivacaine and bupivacaine cohorts [4.5 and 4.6 days, respectively ($P = 0.334$); Fig. 3]. During the first 1 and 2 months after discharge, there were marginally lower odds of all-cause inpatient readmission for the liposomal bupivacaine cohort compared with the bupivacaine cohort ($P = 0.051$ and $P = 0.075$, respectively; (Fig. 3). No statistically significant differences between the liposomal bupivacaine and bupivacaine cohorts were observed for all-cause emergency department visits or outpatient clinic/office visits at 1 and 2 months. For 3 months following discharge, the liposomal bupivacaine

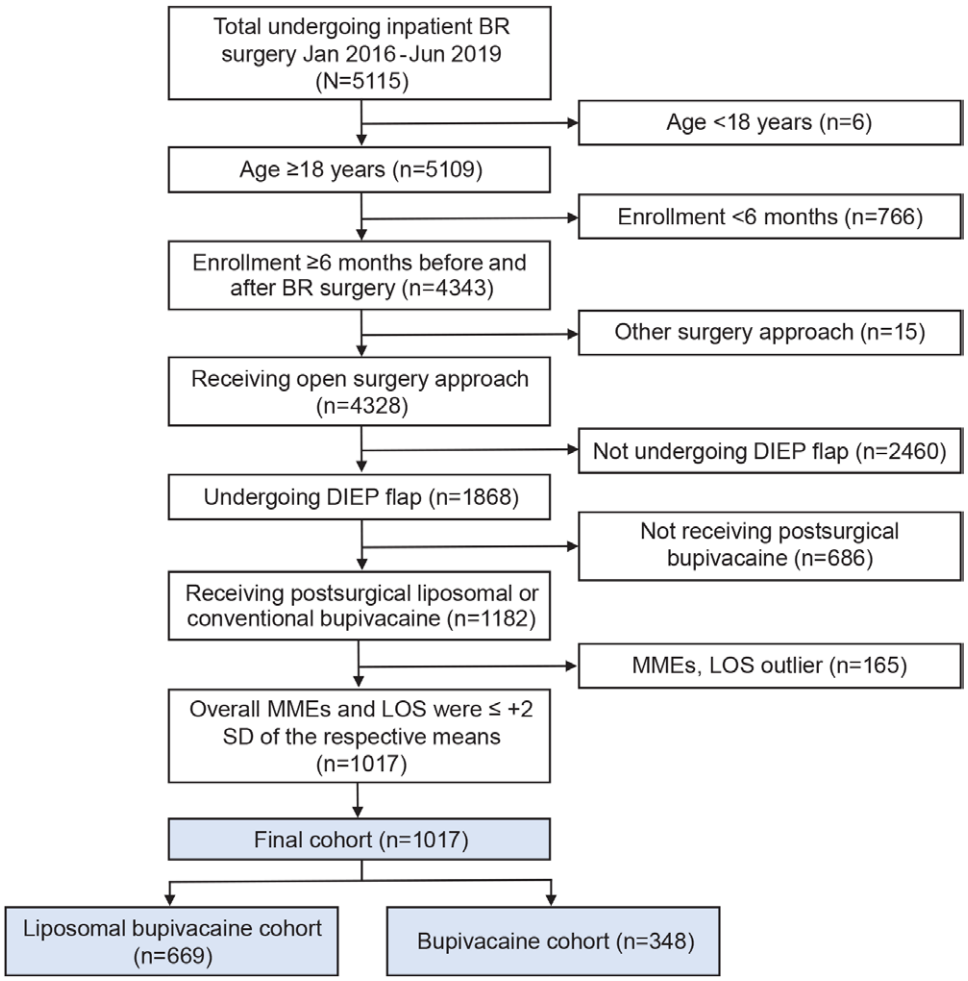

Fig. 1. Sample population for retrospective analysis. BR, breast reconstruction; DIEP, deep inferior epigastric perforator; LOS, length of stay; MME, morphine milligram equivalent; SD, standard deviation.

cohort had significantly lower odds than the bupivacaine cohort for all-cause inpatient readmission [odds ratio (OR), 0.670; $P = 0.046$] and all-cause outpatient clinic/office visits (OR, 0.885; $P = 0.048$). When both cohorts were compared by only pain-related causes of healthcare resource utilization, both outpatient visits and inpatient readmissions were attenuated (n = 2 in both cohorts with inpatient readmissions within 3 months after discharge). However, patients in the liposomal bupivacaine cohort had significantly lower frequency of pain-related emergency department visits compared with the bupivacaine cohort during the 3 months after discharge (OR, 0.55; $P = 0.014$).

DISCUSSION

In this analysis of real-world data, liposomal bupivacaine use in DIEP flap breast reconstruction was associated with lower inpatient opioid intake compared with bupivacaine. The liposomal bupivacaine cohort had lower opioid intake during the first 72 hours after surgery and the perioperative period versus the bupivacaine cohort. LB administration was also associated with fewer inpatient readmissions and outpatient visits for 3 months after discharge than bupivacaine. Using multimodal pain management regimens with nonopioid therapies may reduce the need for opioid prescriptions to manage postoperative pain.[11]

The current results are consistent with prior studies of DIEP flap procedures that reported lower postsurgical pain and opioid consumption with liposomal bupivacaine compared with controls.[21,22] In one retrospective analysis, patients who underwent delayed bilateral DIEP flap breast reconstruction receiving liposomal bupivacaine via TAP block had lower average total intravenous opioids (71.9 versus 130.5 mg; $P = 0.008$) and lower average total opioids (105.6 versus 165.4 mg; $P = 0.005$) versus patients receiving bupivacaine via an elastomeric pump for postoperative analgesia.[22] Further, a prospective study found that patients receiving liposomal bupivacaine for DIEP flap breast reconstruction had lower average intravenous and total opioid use overall than those receiving bupivacaine ($P < 0.002$ for all).[21] Significant reductions in perioperative opioid use with liposomal bupivacaine versus bupivacaine were observed in the current analysis, further supporting the use of liposomal bupivacaine to reduce opioid consumption and provide improved acute pain control after DIEP flap breast reconstruction.

Table 1. Baseline Patient and Hospital Characteristics

	Unweighted			Weighted		
	LB (n = 669)*	Bupivacaine (n = 348)*	Standardized Difference, %	LB, %	Bupivacaine, %	Standardized Difference, %
Age, y	51.7 (9.8)	50.4 (9.2)	−12.9	51.5	51.2	−3.0
Quan-Charlson Comorbidity Index	2.4 (2.5)	2.8 (2.71)	15.4	2.7	2.5	−6.2
Female	669 (100.0)	348 (100.0)	0.0	100.0	100.0	0.0
Hospital Location						
Rural	0 (0.0)	1 (0.3)	NA	NA	NA	NA
Urban	669 (100.0)	347 (99.7)	NA	NA	NA	NA
Teaching Hospital						
Yes	383 (57.3)	88 (25.3)	−68.6	47.2	54.6	14.9
No	259 (38.7)	166 (47.7)	14.6	40.6	34.5	−12.6
Unknown	27 (4.0)	94 (27.0)	66.9	12.3	10.9	−4.2
Hospital Region						
Midwest	3 (0.5)	3 (0.9)	5.1	0.8	0.9	1.3
Northeast	69 (10.3)	38 (10.9)	2.0	10.8	11.0	0.7
South	459 (68.6)	277 (79.6)	25.3	72.2	78.4	14.4
West	138 (20.6)	30 (8.6)	−34.5	16.3	9.7	−19.6
Index Surgery Year						
2016	199 (29.8)	84 (24.1)	−12.7	28.1	31.1	6.4
2017	192 (28.7)	89 (25.6)	−7.0	26.6	23.8	−6.3
2018	219 (32.7)	147 (42.2)	19.7	35.5	36.0	1.1
2019	59 (8.8)	28 (8.1)	−2.8	9.8	9.1	−2.4
Laterality						
Unilateral	295 (44.1)	93 (26.7)	−37.0	39.4	45.3	12.1
Bilateral	374 (55.9)	255 (73.3)	37.0	60.6	54.7	−12.1
History of cancer	459 (68.6)	270 (77.6)	20.4	72.6	66.9	−12.4
History of metastatic cancer	77 (11.5)	52 (14.9)	10.1	13.4	12.9	−1.7
Payer						
Medicaid	3 (0.5)	4 (1.2)	7.9	0.6	0.5	-0.2
Medicare	34 (5.1)	14 (4.0)	−5.1	4.6	3.2	−7.3
Third party	327 (48.9)	266 (76.4)	59.4	58.4	50.6	−15.8
Unknown	305 (45.6)	64 (18.4)	−61.0	36.4	45.6	18.9
Opioid naive	408 (61.0)	152 (43.7)	−35.2	56.7	56.9	0.4

*Values are the mean (SD) for age and Quan-Charlson Comorbidity Index and n (%) for all others.
LB, liposomal bupivacaine; NA, not applicable.

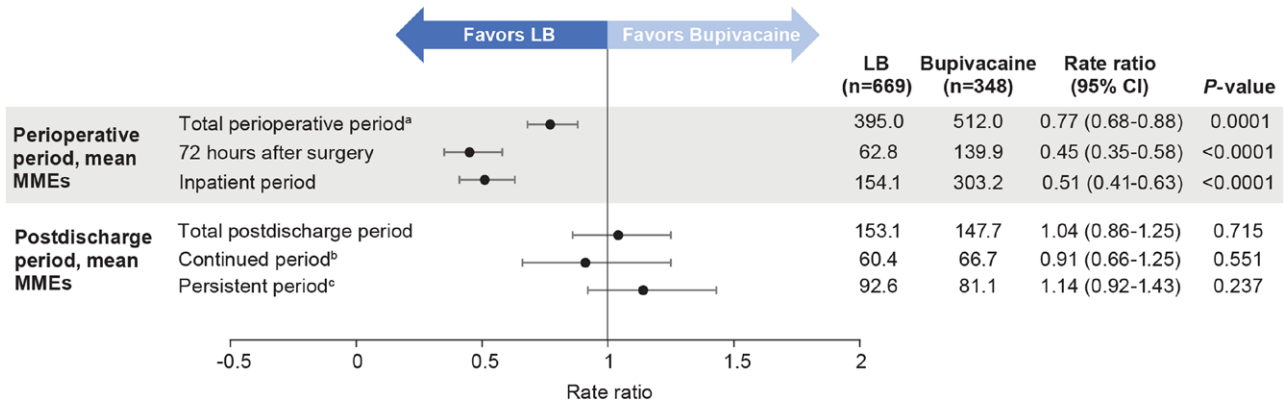

Fig. 2. Opioid use during perioperative and postdischarge periods and hospital LOS. [a]Perioperative period includes 2 weeks before surgery to 2 weeks after discharge. [b]Continued period includes >2 weeks to 3 months after discharge. [c]Persistent period includes 3 months or more to 6 months after discharge. CI, confidence interval; LB, liposomal bupivacaine; LOS, length of stay; MME, morphine milligram equivalent.

The current and previous studies support a reduction in opioid consumption with liposomal bupivacaine in DIEP flap breast reconstruction. Although the MMEs reported in this analysis were higher than those reported in a prior randomized controlled trial and retrospective single-center studies,[15,21,22,26] there are several differences between the previous studies and current analysis that could limit between-study comparisons of MMEs,

Table 2. Opioid Intake during The Perioperative and Postdischarge Period in the Opioid-naive and Opioid-experienced Subgroups

	LB	Bupivacaine	Rate Ratio (95% CI)	*P*
Opioid-naive Subgroup *				
Perioperative period opioid intake, mean MMEs				
Total perioperative period	308.4	359.5	0.86 (0.69–1.06)	0.1548
72 h after surgery	63.7	71.0	0.90 (0.62–1.31)	0.5749
Inpatient	136.3	232.7	0.59 (0.43–0.81)	0.0010
Filled opioid prescriptions, mean MMEs				
Total postdischarge period	97.1	79.0	1.23 (0.89–1.71)	0.2148
Continued period	37.2	19.5	1.91 (1.11–3.28)	0.0200
Persistent period	60.0	59.5	1.01 (0.69–1.48)	0.9657
Opioid-experienced Subgroup †				
Perioperative period opioid intake, mean MMEs				
Total perioperative period	508.4	713.2	0.71 (0.62–0.83)	<0.0001
72 h after surgery	61.5	230.7	0.27 (0.19–0.38)	<0.0001
Inpatient	177.4	396.2	0.45 (0.34–0.59)	<0.0001
Filled opioid prescriptions, mean MMEs				
Total postdischarge period	226.3	238.4	0.95 (0.76–1.18)	0.6411
Continued period	90.9	128.9	0.71 (0.48–1.03)	0.0723
Persistent period	135.4	109.6	1.24 (0.95–1.61)	0.1135

*n = 408 for the LB cohort and n = 152 for the bupivacaine cohort.
†n = 261 for the LB cohort and n = 196 for the bupivacaine cohort.
CI, confidence interval; LB, liposomal bupivacaine; MME, morphine milligram equivalent.

Table 3. Opioid Intake during The Perioperative and Postdischarge Period in the Unilateral and Bilateral Surgery Subgroups

	LB	Bupivacaine	Rate Ratio (95% CI)	*P*
Unilateral Surgery Subgroup *				
Perioperative period opioid intake, mean MMEs				
Total perioperative period	364.9	448.7	0.81 (0.65–1.02)	0.0745
72 h after surgery	69.6	76.6	0.91 (0.58–1.43)	0.6754
Inpatient	158.5	272.3	0.58 (0.40–0.84)	0.0040
Filled opioid prescriptions, mean MMEs				
Total postdischarge period	116.0	127.9	0.91 (0.66–1.25)	0.5475
Continued period	37.3	33.8	1.10 (0.65–1.87)	0.7165
Persistent period	78.7	94.1	0.84 (0.57–1.23)	0.3644
Bilateral Surgery Subgroup †				
Perioperative period opioid intake, mean MMEs				
Total perioperative period	414.5	564.5	0.73 (0.63–0.86)	0.0001
72 h after surgery	58.3	192.3	0.30 (0.22–0.41)	<0.0001
Inpatient	151.2	328.8	0.46 (0.35–0.60)	<0.0001
Filled opioid prescriptions, mean MMEs				
Total postdischarge period	177.1	164.1	1.08 (0.85–1.37)	0.5305
Continued period	75.4	93.9	0.80 (0.55–1.19)	0.2707
Persistent period	101.7	70.3	1.45 (1.10–1.91)	0.0086

*n=295 for the LB cohort and n = 93 for the bupivacaine cohort.
†n=374 for the LB cohort and n = 255 for the bupivacaine cohort.
CI, confidence interval; LB, liposomal bupivacaine; MME, morphine milligram equivalent.

including different study designs (eg, prospective versus retrospective, single-center versus claims databases of ≥300 medical centers), type of DIEP procedure (eg, unilateral versus bilateral, immediate versus delayed), differences in prior opioid exposure within selected patient populations, potential differences in liposomal bupivacaine administration method or dosing (eg, TAP blocks, local infiltration, paravertebral blocks), differing methodology and follow-up durations for opioid consumption measures, and varying components used in the overall study multimodal pain management regimens. Notably, the opioid data in the current analysis likely reflect a wide variety of opioid-prescribing practices across the 300 or more medical centers included in the IQVIA linkage claims databases.

This study also extended postdischarge follow-up, including capture of postdischarge opioid consumption for up to 6 months. One retrospective single-center study analyzed the impact of liposomal bupivacaine via TAP block on postoperative MMEs, but only during the inpatient period after autologous free flap breast

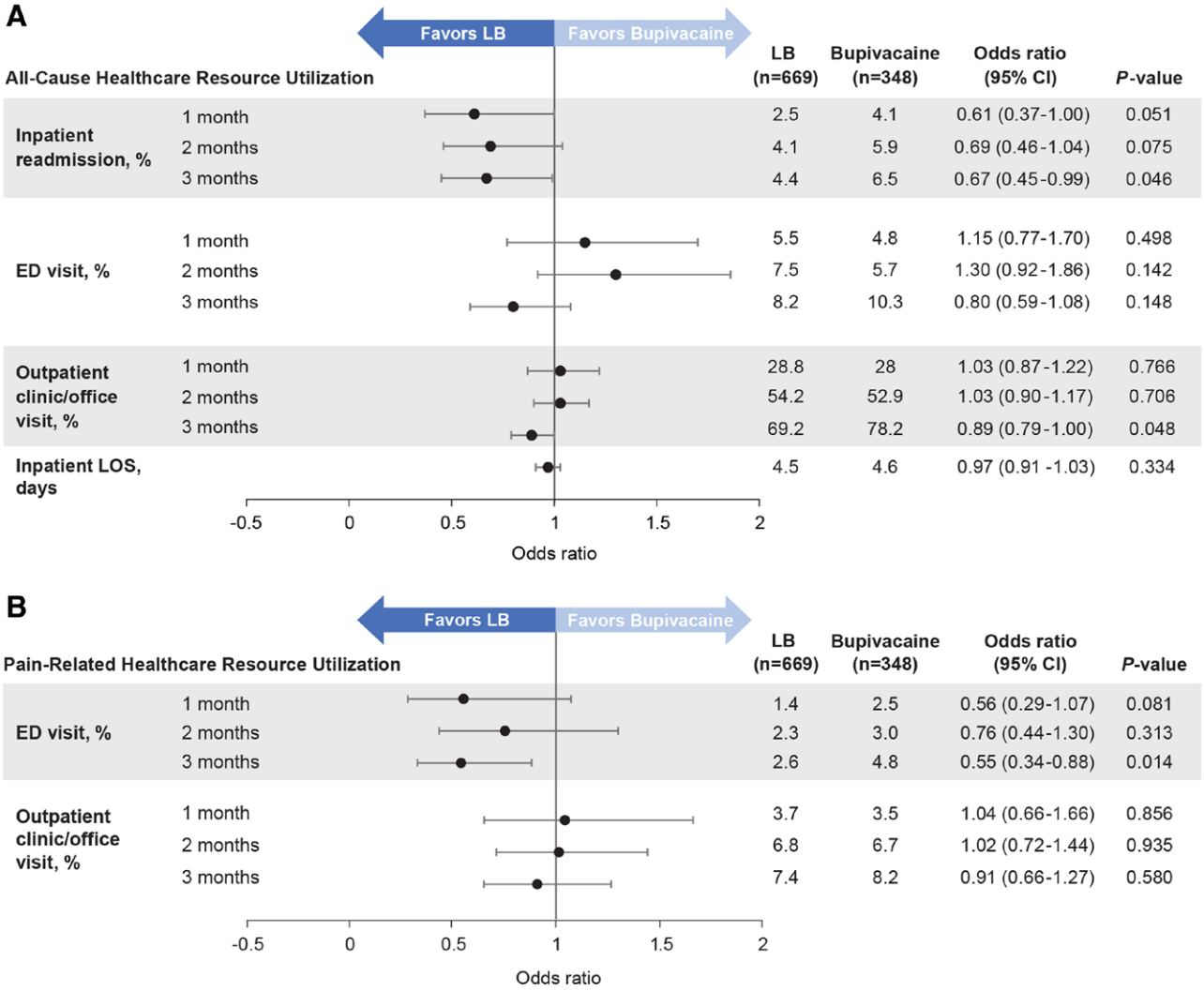

Fig. 3. Postdischarge healthcare resource utilization. A, All-cause postdischarge healthcare resource utilization. B, Pain-related postdischarge healthcare resource utilization. ED, emergency department; LB, liposomal bupivacaine; LOS, length of stay.

reconstruction (including transverse rectus abdominis myocutaneous and DIEP flap procedures).[33] To our knowledge, no other study has examined the impact of liposomal bupivacaine on postdischarge opioid consumption after DIEP. In the current study, there were no significant differences between cohorts in postdischarge opioid consumption, and no patients developed opioid use disorder. The reasons underlying these findings are unknown, although postsurgical recovery options not detailed in the current study may have modified postdischarge opioid consumption.

Subgroup analyses were stratified by prior opioid exposure and laterality because opioid consumption patterns between these subgroups varied. For example, a previous study determined that patients who underwent bilateral breast reconstruction were more likely to fill prescriptions with higher daily MMEs versus those undergoing unilateral reconstruction (74.5 versus 55.2 mg; $P = 0.02$).[12] In the current study, reductions in perioperative opioid consumption in the liposomal bupivacaine versus bupivacaine cohort were generally sustained when analyzed by subgroups of prior opioid exposure and surgery laterality, notably in the opioid-experienced and bilateral surgery subgroups. This may be due to the bilateral subgroup having increased pain versus the unilateral subgroup because of more surgical sites.

Analgesic approaches after DIEP flap breast reconstruction may impact LOS, emergency department visits, and inpatient readmissions. Of note, LOS with liposomal bupivacaine in the current analysis was comparable to prior studies of liposomal bupivacaine for DIEP flap procedures (4.5 versus 3–5 days[15,21,22]). Nevertheless, the liposomal bupivacaine cohort in the current analysis had reductions in all-cause postdischarge inpatient readmissions and outpatient/office visits 3 months after discharge versus the bupivacaine cohort. The reasons for observed differences in inpatient readmissions and outpatient/office visits 3 months after discharge are not immediately clear and are likely not directly related to prolonged opioid use given prescribed MMEs in the postdischarge

period were similar between cohorts, although other unknown factors due to lower opioid intake during the perioperative period cannot be ruled out. The reduction in all-cause inpatient readmissions with liposomal bupivacaine is important, given the costs associated with these events (eg, the Agency for Healthcare Research and Quality has estimated the average cost of a single hospital readmission to be $16,300).[34]

In the current analysis, pain-related emergency department visits during the 3 months after discharge were increased in the bupivacaine cohort compared with the liposomal bupivacaine cohort, suggesting adequacy of postsurgical pain control may underlie healthcare resource utilization after DIEP flap procedures. Consistently, pain-related diagnoses were previously identified as the most common reason for an emergency department visit after a mastectomy, accounting for 28% of total emergency department visits for a subgroup of patients who underwent immediate breast reconstruction.[35] Emergency department visits are associated with healthcare cost burden, with the Agency for Healthcare Research and Quality estimating the average cost per emergency department visit to be $530.[36] Overall, the potential impact of liposomal bupivacaine analgesia on healthcare resource utilization outcomes in DIEP flap breast reconstruction warrants additional investigation of long-term pain recovery after surgery, which may be influenced by adequate postsurgical pain control and potentially other factors such as postsurgical complications.

The limitations of this analysis are primarily related to the inherent limitations of real-world claims databases. This study examined postdischarge opioid use by filled prescriptions; however, the databases do not include information regarding whether prescriptions were consumed, which could overestimate the amount of MMEs reported for the postdischarge period. Additionally, some variables that may have affected postsurgical pain management, including concurrent procedures (eg, use of ultrasound guidance), information on enhanced recovery after surgery protocols, and procedural details (eg, conjoined flaps), are not available. Although this study assessed reductions in opioid use by MMEs, pain scores are not captured in the IQVIA linkage claims databases, which prevented direct comparison of perioperative and postdischarge pain control to complement opioid consumption observations. The IQVIA linkage claims databases also do not capture the administration methods used for liposomal bupivacaine or bupivacaine (eg, local infiltration versus TAP blocks), and dosing information is missing or incompletely captured, which could affect the reported outcomes. Although most liposomal bupivacaine use likely reflects US Food and Drug Administration–approved administration modalities for liposomal bupivacaine, other routes of administration cannot be ruled out, and the current results likely reflect the mean effect of various routes of administration. We also note that some baseline variables (eg, laterality) had moderate standardized differences (ie, > 10% to < 20%), likely due to limited statistical power. Nevertheless, subgroup analysis by laterality suggested somewhat comparable results for postsurgical opioid use. Residual confounding may have occurred in comparisons between cohorts. Finally, it is possible that the finite follow-up duration of this analysis may have impacted the ability to detect opioid-related adverse events or cases of opioid use disorder.

Despite limitations inherent to claims databases, this analysis has several strengths. The IQVIA linkage claims databases provide diverse data from a large real-world sample, with patient-level information from more than 300 healthcare facilities across the United States. Deidentified patient records contain data from hospitals, physician offices, and pharmacies enabling analysis of clinical, safety, healthcare resource utilization, and economic outcomes. Patients were followed up longitudinally to allow for postdischarge outcomes analysis as opposed to most previous studies, which did not examine postdischarge outcomes for DIEP flap breast reconstruction. The current analysis examined opioid use through 6 months after surgery and healthcare resource utilization through 3 months after surgery, contributing data regarding both clinical and economic burden to understanding long-term pain management for patients undergoing breast reconstruction.

In conclusion, this real-world analysis demonstrated that liposomal bupivacaine was associated with lower opioid requirements than conventional bupivacaine, independently of nonopioid pain regimens, in the perioperative period for DIEP flap breast reconstruction. The association was more pronounced in patients with bilateral surgery and a history of opioid exposure, although the implication of these subgroup associations remains unknown and future verification is needed. Reductions in postdischarge all-cause inpatient readmissions and pain-related emergency department visits with liposomal bupivacaine also support potential reductions in healthcare cost burden. Future studies are warranted to further expand on the current results.

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DISCLOSURES

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REFERENCES

1. American Society of Plastic Surgeons. 2018 plastic surgery statistics report. Available at https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf. Accessed June 1, 2023.

2. American Society of Plastic Surgeons. 2020 plastic surgery statistics report. Available at https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf. Accessed June 1, 2023.
3. Hedegard W, Niell B, Specht M, et al. Breast reconstruction with a deep inferior epigastric perforator flap: imaging appearances of the normal flap and common complications. *AJR Am J Roentgenol*. 2013;200:W75–W84.
4. Yueh JH, Slavin SA, Adesiyun T, et al. Patient satisfaction in postmastectomy breast reconstruction: a comparative evaluation of DIEP, TRAM, latissimus flap, and implant techniques. *Plast Reconstr Surg*. 2010;125:1585–1595.
5. De Oliveira GS, Jr, Bialek JM, Nicosia L, et al. Lack of association between breast reconstructive surgery and the development of chronic pain after mastectomy: a propensity matched retrospective cohort analysis. *Breast*. 2014;23:329–333.
6. Roth RS, Qi J, Hamill JB, et al. Is chronic postsurgical pain surgery-induced? A study of persistent postoperative pain following breast reconstruction. *Breast*. 2018;37:119–125.
7. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in us adults. *JAMA Surg*. 2017;152:e170504.
8. Jiang X, Orton M, Feng R, et al. Chronic opioid usage in surgical patients in a large academic center. *Ann Surg*. 2017;265:722–727.
9. Fiore JF, Jr, El-Kefraoui C, Chay MA, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet*. 2022;399:2280–2293.
10. Herzig SJ, Stefan MS, Pekow PS, et al. Risk factors for severe opioid-related adverse events in a national cohort of medical hospitalizations. *J Gen Intern Med*. 2020;35:538–545.
11. Malik KM, Imani F, Beckerly R, et al. Risk of opioid use disorder from exposure to opioids in the perioperative period: a systematic review. *Anesth Pain Med*. 2020;10:e101339.
12. Marcusa DP, Mann RA, Cron DC, et al. Prescription opioid use among opioid-naive women undergoing immediate breast reconstruction. *Plast Reconstr Surg*. 2017;140:1081–1090.
13. Gort N, van Gaal BGI, Tielemans HJP, et al. Positive effects of the enhanced recovery after surgery (ERAS) protocol in DIEP flap breast reconstruction. *Breast*. 2021;60:53–57.
14. Linder S, Walle L, Loucas M, et al. Enhanced recovery after surgery (ERAS) in DIEP-flap breast reconstructions-a comparison of two reconstructive centers with and without eRAS-protocol. *J Pers Med*. 2022;12:347.
15. Haddock NT, Garza R, Boyle CE, et al. Defining enhanced recovery pathway with or without liposomal bupivacaine in DIEP flap breast reconstruction. *Plast Reconstr Surg*. 2021;148:948–957.
16. Rendon JL, Borrell-Vega J, Reyes JC, et al. Evaluating the efficacy of two regional pain management modalities in autologous breast reconstruction. *Plast Reconstr Surg Glob Open*. 2022;10:e4010.
17. Odom EB, Mehta N, Parikh RP, et al. Paravertebral blocks reduce narcotic use without affecting perfusion in patients undergoing autologous breast reconstruction. *Ann Surg Oncol*. 2017;24:3180–3187.
18. Batdorf NJ, Lemaine V, Lovely JK, et al. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2015;68:395–402.
19. ElHawary H, Abdelhamid K, Meng F, et al. Erector spinae plane block decreases pain and opioid consumption in breast surgery: systematic review. *Plast Reconstr Surg Glob Open*. 2019;7:e2525.
20. Knackstedt R, Oliver JD, Gatherwright J. Optimizing postoperative pain control in autologous breast reconstruction: a systematic review. *J Reconstr Microsurg*. 2020;36:480–485.
21. Gatherwright J, Knackstedt RW, Ghaznavi AM, et al. Prospective, randomized, controlled comparison of bupivacaine versus liposomal bupivacaine for pain management after unilateral delayed deep inferior epigastric perforator free flap reconstruction. *Plast Reconstr Surg*. 2018;141:1327–1330.
22. Knackstedt R, Gatherwright J, Ghaznavi A, et al. Comparison of local anesthetic infusion pump bupivacaine versus transversus abdominis plane (TAP) block liposomal bupivacaine for pain management after bilateral deep inferior epigastric perforator free flap reconstruction. *J Plast Reconstr Aesthet Surg*. 2017;70:1779–1781.
23. Afonso A, Oskar S, Tan KS, et al. Is enhanced recovery the new standard of care in microsurgical breast reconstruction? *Plast Reconstr Surg*. 2017;139:1053–1061.
24. ElHawary H, Joshi GP, Janis JE. Practical review of abdominal and breast regional analgesia for plastic surgeons: evidence and techniques. *Plast Reconstr Surg Glob Open*. 2020;8:e3224.
25. Ha AY, Keane G, Parikh R, et al. The analgesic effects of liposomal bupivacaine versus bupivacaine hydrochloride administered as a transversus abdominis plane block after abdominally based autologous microvascular breast reconstruction: a prospective, single-blind, randomized, controlled trial. *Plast Reconstr Surg*. 2019;144:35–44.
26. Nguyen L, Glassman GE, Afshari A, et al. Double-blinded randomized control trial comparing liposomal bupivacaine and plain bupivacaine in transversus abdominis plane for deep inferior epigastric artery perforator (DIEP) flap breast reconstruction. *Plast Reconstr Surg*. 2024;153:543–551.
27. Little A, Brower K, Keller D, et al. A cost-minimization analysis evaluating the use of liposomal bupivacaine in reconstructive plastic surgery procedures. *Plast Reconstr Surg*. 2019;143:1269–1274.
28. IQVIA. Real world data and life sciences research: Data sources that are transforming the way we work. Available at https://www.iqvia.com/locations/united-states/library/white-papers/real-world-data-and-life-sciences-research. Accessed November 9, 2021.
29. United States Department of Health and Human Services. CMS place of service code set. Available at https://www.hhs.gov/guidance/document/cms-place-service-code-set. Updated September 2023. Accessed November 6, 2023.
30. Tirotta CF, Lin JH, Tran MH. Effectiveness of liposomal bupivacaine compared with standard-of-care measures in pediatric cardiothoracic surgery: a Retrospective cohort study. *J Cardiothorac Vasc Anesth*. 2021;35:3681–3687.
31. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679.
32. Alberts M, Chen YW, Lin JH, et al. Risks of stroke and mortality in atrial fibrillation patients treated with rivaroxaban and warfarin. *Stroke*. 2020;51:549–555.
33. Nelson JA, Polanco TO, Shamsunder MG, et al. Perioperative inpatient opioid consumption following autologous free-flap breast reconstruction patients: An examination of risk and patient-reported outcomes. *Ann Surg Oncol*. 2021;28:7823–7833.
34. Agency for Healthcare and Research Quality. Characteristics of 30-day all-cause hospital readmissions, 2016-2020. Statistical brief #304. Available at https://hcup-us.ahrq.gov/reports/statbriefs/sb304-readmissions-2016-2020.jsp. Accessed December 14, 2023.
35. Nasser JS, Huetteman HE, Chung TT, et al. Unplanned emergency department visits within 30 days of mastectomy and breast reconstruction. *Plast Reconstr Surg*. 2018;142:1411–1420.
36. Agency for Healthcare and Research Quality. Costs of emergency department visits in the United States, 2017. Statistical brief #268. Available at https://hcup-us.ahrq.gov/reports/statbriefs/sb268-ED-Costs-2017.jsp. Accessed December 14, 2023.