Liposomal Bupivacaine Does Not Reduce Inpatient Opioid Prescription or Related Complications after Knee Arthroplasty

A Database Analysis

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ABSTRACT

Background: Although some trials suggest benefits of liposomal bupivacaine, data on real-world use and effectiveness is lacking. This study analyzed the impact of liposomal bupivacaine use (regardless of administration route) on inpatient opioid prescription, resource utilization, and opioid-related complications among patients undergoing total knee arthroplasties with a peripheral nerve block. It was hypothesized that liposomal bupivacaine has limited clinical influence on the studied outcomes.

Methods: The study included data on 88,830 total knee arthroplasties performed with a peripheral nerve block (Premier Healthcare Database 2013 to 2016). Multilevel multivariable regressions measured associations between use of liposomal bupivacaine and (1) inpatient opioid prescription (extracted from billing) and (2) length of stay, cost of hospitalization, as well as opioid-related complications. To reflect the difference between statistical and clinical significance, a relative change of −15% in outcomes was assumed to be clinically important.

Results: Overall, liposomal bupivacaine was used in 21.2% (n = 18,817) of patients that underwent a total knee arthroplasty with a peripheral nerve block. Liposomal bupivacaine use was not associated with a clinically meaningful reduction in inpatient opioid prescription (group median, 253 mg of oral morphine equivalents, adjusted effect −9.3% CI −11.1%, −7.5%; $P < 0.0001$) and length of stay (group median, 3 days, adjusted effect −8.8% CI −10.1%, −7.5%; $P < 0.0001$) with no effect on cost of hospitalization. Most importantly, liposomal bupivacaine use was not associated with decreased odds for opioid-related complications.

Conclusions: Liposomal bupivacaine was not associated with a clinically relevant improvement in inpatient opioid prescription, resource utilization, or opioid-related complications in patients who received modern pain management including a peripheral nerve block. **(Anesthesiology 2018; 129:689-99)**

THE management of pain after total knee arthroplasty poses a special challenge to perioperative physicians. Although opioid based regimens remain the cornerstone of postoperative pain control, a multimodal approach involving a combination of opioids, nonopioid analgesics, and regional anesthetic techniques is increasingly being used.[1–4] By combining two or more analgesic agents with different mechanisms of action, a multimodal approach should provide adequate pain relief while reducing opioid requirements and opioid-related adverse effects.[1,3]

In this context, local anesthetics have provided the basis for the performance of peripheral nerve blocks or infiltration techniques, which have been highly effective in reducing pain after joint arthroplasties.[5–7] However, their effectiveness has been limited by a relatively short period of action. Catheter approaches have provided the ability to prolong the infusion of local anesthetics but require additional equipment and maintenance and in rare occasions are associated with complications such as infections and inpatient falls.[8,9] A recently developed therapy, liposomal bupivacaine, showed promise in addressing these shortfalls. By encapsulating a local anesthetic (bupivacaine) with a lipid-based structure, the local anesthetic is released slowly over time. Thus, liposomal bupivacaine potentially offers

Editor's Perspective

What We Already Know about This Topic

- The need for long-duration nonopioid pain relief after total knee arthroplasty has driven multimodal analgesic regimens, some of which include the administration of liposomal bupivacaine
- It is unclear whether the use of liposomal bupivacaine is reliably associated with improvements in clinical or resource outcomes

What This Manuscript Tells Us That Is New

- Retrospective analysis of a national observational data set showed that liposomal bupivacaine use for total knee arthroplasty is increasing
- Liposomal bupivacaine use was not associated with clinically meaningful reductions in inpatient opioid use, opioid-related complications, or resource utilization in patients who received modern pain management including a peripheral nerve block

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 623. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. An abstract of this study was presented as a poster at the 42nd Annual Regional Anesthesiology and Acute Pain Medicine Meeting in San Francisco, California, April 6 to 8, 2017.

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the ease of a local infiltration technique along with the longevity associated with a continuous peripheral nerve block. However, its utility in clinical practice remains debated.[10,11] Liposomal bupivacaine has been approved by the U.S. Food and Drug Administration for use in local infiltration and interscalene brachial plexus blocks,[12] although it is not (yet) recommended for use in other peripheral nerve blocks or for neuraxial or intraarticular use. Therefore, although off-label use may indeed occur, we expect most use of liposomal bupivacaine to be in line with its Food and Drug Administration–approved route.

Although several studies in various general patient populations have shown encouraging results, a number of publications have suggested a limited benefit.[13–16] Moreover, previous studies have been limited by several factors, including nonequivalence between comparison groups as well as not following best practices with respect to multimodal analgesia techniques. Moreover, these studies have typically been limited to a single institution, so that population-based data representing everyday practice using liposomal bupivacaine and its effectiveness to reduce opioid use and opioid-related adverse effects are lacking.

Therefore, we used a large national database to study the impact of liposomal bupivacaine (regardless of route of administration) in patients undergoing a total knee arthroplasty, with particular focus on those undergoing the procedure with the utilization of a peripheral nerve block. We analyzed the effect of liposomal bupivacaine use on outcomes. Our primary outcome was inpatient opioid prescription (extracted from billing). Secondary outcomes were opioid-related complications, hospitalization cost, and length of hospital stay. We hypothesized that (1) liposomal bupivacaine was used in the minority of cases, (2) utilization was increasing over time, and (3) liposomal bupivacaine has limited clinical influence on the studied outcomes in patients who received multimodal analgesia including peripheral nerve blocks.

Materials and Methods

Data Source, Study Design, and Study Sample

This retrospective cohort study was considered exempt by the Institutional Review Boards of the Mount Sinai Hospital (New York, New York; approval No. 14-00647) and the Hospital for Special Surgery (New York, New York; approval No. 2012-050) due to the deidentified nature of the data. The data source was the nationwide all-payer Premier Healthcare database (Premier Inc., USA), which contains detailed billing information on 20 to 25% of U.S. hospitalizations.[17,18] The study sample was created using the International Classification of Diseases, Ninth Revision (ICD-9) procedure code for primary knee replacement (81.54). The cohort contained patients undergoing surgery from January 1, 2013, to December 31, 2016. From this sample, we selected patients that received a peripheral nerve block (n = 100,795). Patients were excluded in case of nonelective procedures (n = 1,852), unknown discharge status (n = 9), an outpatient procedure (n = 477), treatment at a hospital performing less than 30 total knee arthroplasties (to ensure sufficient sample size per hospital; n = 715),[19] absent billing for inpatient opioid prescription (n = 4,268), and inpatient opioid prescription above the 95th percentile (n = 4,644). The latter two exclusion criteria were applied to account for extremes and potentially unreliable billing for opioids. The Premier data have been used in numerous population-based studies examining health outcomes.[20–22] After applying the exclusion criteria, there were no missing data for any variable of interest. We specifically aimed to perform our main analyses in a cohort of patients receiving peripheral nerve blocks to analyze the impact of liposomal bupivacaine in a setting in which state-of-the-art pain management was practiced; this decision was made *a priori*.

Study Variables

An analysis plan was created *a priori* that identified all relevant study variables including the main effect of interest and outcomes. The main effect of interest was the use of liposomal bupivacaine; a binary variable was created based on billing for liposomal bupivacaine. Unfortunately, using the Premier data set, we were not able to differentiate between the various routes of liposomal bupivacaine administration. However, we expect most liposomal bupivacaine to be used in line with its Food and Drug Administration–approved administration modality (local infiltration). Use of a peripheral nerve block was determined by a combination of billed charges and Current Procedural Terminology codes as previously defined.[23]

The primary outcome was inpatient opioid prescription. This was extracted from billing for opioids and converted to oral morphine equivalents using the Lexicomp "opioid agonist conversion" and the GlobalRPH "opioid analgesic converter."[24,25] We used this as a proxy for opioid administration, recognizing that this may lead to an overestimation because not everything billed for may be actually administered. This bias, however, is minimized because we expect this likely overestimation to be independent of liposomal bupivacaine use and thus affect both groups equally.

Secondary outcomes were length and cost of hospitalization and opioid-related complications including respiratory, gastrointestinal, central nervous system, genitourinary, and "other" (composite of ICD-9 codes for postoperative bradycardia, rash or itching, drugs causing adverse effects with therapeutic use, and fall from bed) complications.[26] Inpatient opioid prescription (in mg oral morphine equivalents) was categorized into prescription totals for the entire hospitalization and totals for the day of surgery (day 0), the day after (day 1), and the subsequent days (day 1+). Cost

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of hospitalization was adjusted for inflation and reported in 2016 U.S. dollars. Length of stay was reported in days.

Patient demographics included age, sex, and race (white, black, other). Healthcare-related variables included insurance type (commercial, Medicaid, Medicare, uninsured, other), hospital location (urban, rural), hospital size (less than 300, 300 to 499, at least 500 beds), hospital teaching status, and the annual number of total knee arthroplasties performed per hospital. Procedure-related variables included the year of the procedure, the use of neuraxial anesthesia, the use of general anesthesia, patient-controlled analgesia, and use of nonopioid analgesics (IV acetaminophen, gabapentin/pregabalin [gabapentinoids], nonsteroidal antiinflammatory drugs [NSAIDs], cyclooxygenase-2 inhibitors, and ketamine). Overall comorbidity burden was assessed using the Quan *et al.* adaptation of the Charlson–Deyo Comorbidity Index.[27] In addition, we included separate variables indicating substance use/abuse (including smoking), chronic pain conditions, and psychiatric comorbidity variables because they may influence particularly inpatient opioid prescription. The definitions of these variables can be found in Supplemental Digital Content 1 (http://links.lww.com/ALN/B719).

As is typical when using population-based data (*i.e.*, data not specifically collected for any specific study), variables may be under- or overreported. This holds particularly true for inpatient opioid utilization because the amount billed for may not necessarily reflect the amount administered; thus, a potential overestimation may occur. However, numbers from the current study fall in line with those reported in other studies.[28–30] For opioid-related complications, we expect an underreporting because they are defined using ICD-9 codes for which a limited number of fields exist per case. We expect cost and length of stay to be accurate because that is the main focus of the Premier Healthcare data set (*i.e.*, economic benchmarking for hospitals).[18]

Statistical Analysis

Univariable associations between liposomal bupivacaine use and study variables were analyzed using the chi-square test and *t* test for categorical and continuous variables, respectively. Multilevel, multivariable regression models were fit to measure associations between liposomal bupivacaine use and outcomes. Multilevel models account for correlation of patients within hospitals (*i.e.*, patients are "nested" within each hospital) and fit one regression line for each hospital, based on all patients within a given hospital.[31] This adjustment is necessary because patients within hospitals are correlated as they may experience similar care (*e.g.*, equal chance of liposomal bupivacaine for patients within the same hospital).

Covariates used in the multilevel models were chosen based on clinical importance and/or univariable significance at the $P < 0.15$ level.[32] The final covariates in the model are age, hospital-specific annual volume of total knee arthroplasties, hospital size, Charlson–Deyo Index, sex, race, year, insurance type, hospital teaching status, hospital location, general anesthesia use, neuraxial anesthesia use, liposomal bupivacaine, NSAIDs, cyclooxygenase-2 inhibitors, ketamine, gabapentinoids, patient-controlled analgesia, IV acetaminophen, and the comorbidity variables indicating substance use/abuse, chronic pain conditions, and psychiatric conditions. Full model coefficients can be found in Supplemental Digital Content 2 (http://links.lww.com/ALN/B720). Effect estimates are reported as adjusted odds ratios with Bonferroni-adjusted *P* values and 95% CI, which will reduce the risk of type I errors, whereas the likelihood of type II errors may be increased.[33] Model discrimination was evaluated using the c-statistic (area under the receiver operating curve). A c-statistic value of 0.7 or higher shows good discrimination.[34]

All analyses were done using the PROC GLIMMIX procedure in SAS v9.4 statistical software (SAS Institute, USA). For the continuous outcomes of inpatient opioid prescription, cost of hospitalization, and length of stay, the γ distribution with a log-link function was used as these variables are skewed.[35,36] Effect estimates for these outcomes are reported as percentage change and confidence intervals.

The PROC GLIMMIX procedure was additionally used to determine the intraclass correlation coefficient, which estimates the percentage of variation in liposomal bupivacaine use that is accounted for by hospitals included in our study.[37] A high percentage would indicate that liposomal bupivacaine use is mainly determined by hospital-level factors.

Sensitivity Analysis

We performed a sensitivity analysis to address the possible issue of confounding by indication with patients receiving liposomal bupivacaine because of greater pain and thus more likely to have increased inpatient opioid prescription. To address this potential bias, the sensitivity analysis was performed in a cohort restricted to hospitals with at least 50% liposomal bupivacaine use, which may indicate that these hospitals have a perioperative pain protocol that includes liposomal bupivacaine, hence negating the idea of confounding by indication.

Statistical and Clinical Significance

As recommended, we judged our inpatient opioid prescription and resource utilization results in respect to their clinically meaningful significance by *a priori* designating an at least −15% reduction of the reported outcome as clinically meaningful. Authors studying opioid-related complications have suggested that this reduction should be at least 25%.[38] Thus, our threshold should be considered less stringent. Statistical significance is reported at the traditional $P < 0.05$ value.

A Priori versus Post Hoc *Analyses*

Through the course of the peer-review process, we made adjustments to our initial *a priori* specified analyses. Specifically, we

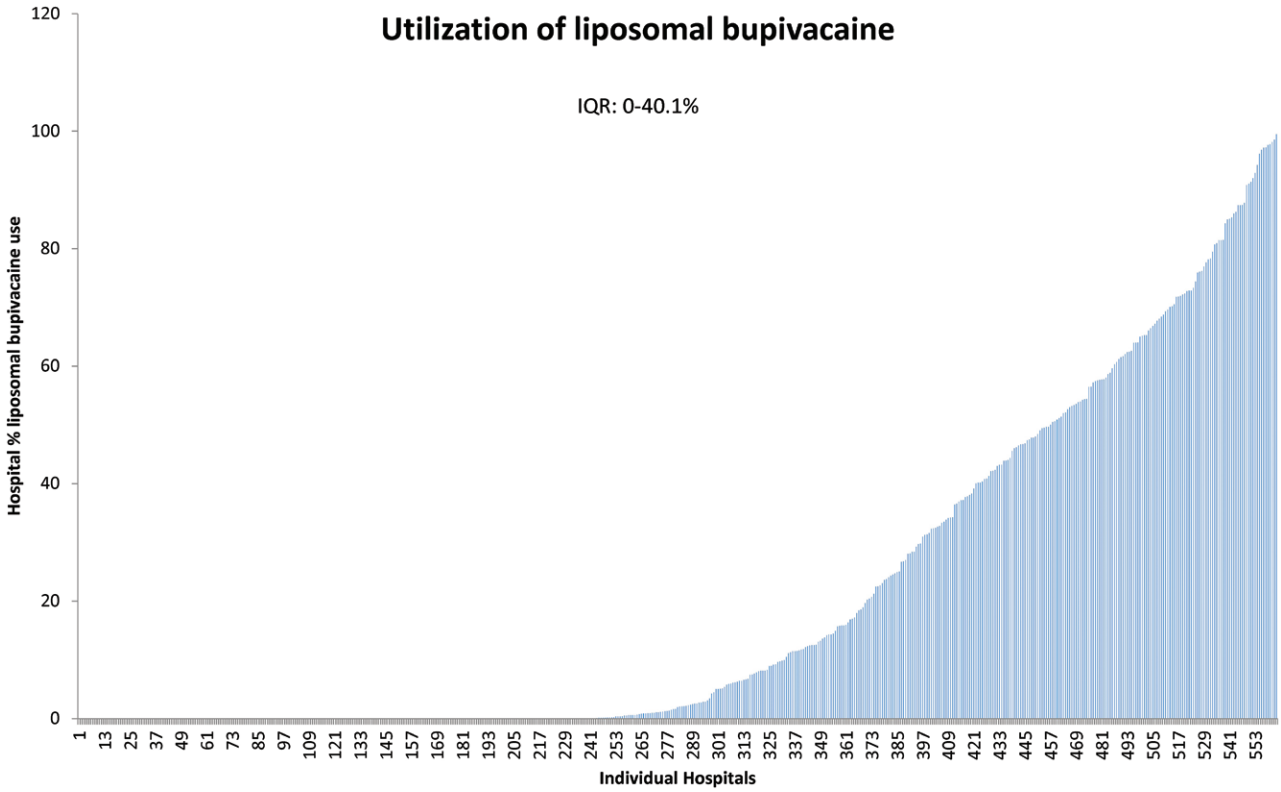

Fig. 1. Interhospital variation (with interquartile range [IQR]) in liposomal bupivacaine use.

performed the same analyses as mentioned above in two separate cohorts: (1) patients undergoing total knee arthroplasty with a peripheral nerve block and use of general anesthesia and (2) patients undergoing total knee arthroplasty with a peripheral nerve block and use of neuraxial anesthesia.

The reasoning behind these additional analyses is that we expect a more pronounced effect of liposomal bupivacaine among patients with a higher (general anesthesia patients) compared to a lower (neuraxial anesthesia patients) baseline opioid utilization. Use of general and neuraxial anesthesia is defined through the Premier billing file as previously described.[23] An additional analysis was performed to assess whether using the individual comorbidities making up the index in our multivariable models would produce different results compared to the use of the Charlson–Deyo index itself.

Results

We identified 88,830 hospitalizations from 2013 to 2016 during which a total knee arthroplasty was performed using a peripheral nerve block. Liposomal bupivacaine was used in 21.2% (n = 18,817) of patients with substantial interhospital variation in liposomal bupivacaine use ranging from 0 to 99.5% (interquartile range: 0 to 40.1%) (fig. 1). In addition, use of liposomal bupivacaine increased over time from 7.1% in 2013 to 25.5% in 2016, respectively.

Table 1 shows patient demographics, healthcare-related, and procedure-related variables and comorbidities by use of liposomal bupivacaine. Differences in patient demographics, comorbidities, and insurance type were small between those receiving and not receiving liposomal bupivacaine. Use of liposomal bupivacaine was higher in urban, small- and medium-sized, and nonteaching hospitals. Institutions using liposomal bupivacaine performed a higher number of total knee arthroplasties on an annual basis. Of note, patients who received liposomal bupivacaine also received other nonopioid analgesic medication significantly more often than the control group, except for NSAIDs and ketamine.

Table 2 details the prevalence of complications and provides information on inpatient opioid prescription, cost and length of hospitalization, and outcomes from multivariable models. In general, absolute rates of complications in patients who received liposomal bupivacaine were marginally lower compared to those who did not receive liposomal bupivacaine. Univariable results showed that patients in the liposomal bupivacaine group had lower inpatient opioid prescription (190 *vs.* 272 median mg oral morphine equivalents), length of stay (2 *vs.* 3 median days), and cost of hospitalization ($15,013 *vs.* $15,810 median dollars). However, when controlling for relevant covariates, the use of liposomal bupivacaine was associated with no clinically meaningful reduction in overall inpatient opioid prescription (adjusted effect, −9.3%; CI −11.1%, −7.5%; $P < 0.0001$) and length of stay (−8.8%; CI −10.1%, −7.5%; $P < 0.0001$) and a nonsignificant increase in cost of hospitalization (+2.2%; CI −0.1%, +4.6%; $P = 0.0900$).

Table 1. Patient Demographics, Healthcare-related, Procedure-related, and Comorbidity-related Variables (Chi-Square and *t* Tests for Categorical and Continuous Variables, Respectively) by Liposomal Bupivacaine Use in the Peripheral Nerve Block Cohort

	Use of Liposomal Bupivacaine, n (%)		
	Yes (n = 18,817)	No (n = 70,013)	*P* Value
Patient demographics			
Age (yr), median (IQR)	67 (60–73)	67 (60–73)	0.0032
Sex			0.8101
Female	11,588 (61.6)	43,183 (61.7)	
Male	7,229 (38.4)	26,830 (38.3)	
Race/ethnicity			< 0.0001
White	15,537 (82.6)	55,839 (79.8)	
Black	2,184 (11.6)	5,478 (7.8)	
Other	1,096 (5.8)	8,696 (12.4)	
Comorbidity-related			
Charlson–Deyo comorbidity index (categorized)			< 0.0001
0	13,843 (73.6)	50,207 (71.7)	
1	3,540 (18.8)	13,853 (19.8)	
2	988 (5.3)	3,900 (5.6)	
2+	446 (2.4)	2,053 (2.9)	
Substance use/abuse	1,362 (7.2)	5,413 (7.7)	0.0236
Pain conditions	3,191 (17.0)	12,698 (18.1)	0.0002
Psychiatric conditions	3,762 (20.0)	15,498 (22.1)	< 0.0001
Procedure-related			
Year of procedure			< 0.0001
2013	1,300 (6.9)	16,946 (24.2)	
2014	4,620 (24.6)	16,799 (24.0)	
2015	6,629 (35.2)	18,011 (25.7)	
2016	6,268 (33.3)	18,257 (26.1)	
General anesthesia use	10,260 (54.5)	33,021 (47.2)	< 0.0001
Neuraxial anesthesia use	1,773 (9.4)	16,140 (23.1)	< 0.0001
NSAID use	10,748 (57.1)	39,573 (56.5)	0.1429
Cox-2 inhibitor use	11,095 (59.0)	32,771 (46.8)	< 0.0001
Ketamine use	1,127 (6.0)	5,640 (8.1)	< 0.0001
Gabapentinoids use	9,011 (47.9)	22,213 (31.7)	< 0.0001
IV acetaminophen use	7,514 (39.9)	19,163 (27.4)	< 0.0001
Patient-controlled analgesia use	237 (1.3)	6,019 (8.6)	< 0.0001
Healthcare-related			
Insurance type			< 0.0001
Commercial	6,652 (35.4)	24,553 (35.1)	
Medicaid	343 (1.8)	2,319 (3.3)	
Medicare	11,238 (59.7)	40,704 (58.1)	
Uninsured	33 (0.2)	163 (0.2)	
Unknown	551 (2.9)	2,274 (3.2)	
Hospital location			< 0.0001
Rural	726 (3.9)	8,385 (12.0)	
Urban	18,091 (96.1)	61,628 (88.0)	
Hospital size			< 0.0001
< 300 beds	8,885 (47.2)	28,281 (40.4)	
300–499 beds	6,880 (36.6)	18,796 (26.8)	
≥ 500 beds	3,052 (16.2)	22,936 (32.8)	
Hospital teaching status			< 0.0001
Nonteaching	12,572 (66.8)	37,720 (53.9)	
Teaching	6,245 (33.2)	32,293 (46.1)	
Annual total knee arthroplasties per hospital, median (IQR)	515 (331–770)	503 (276–774)	< 0.0001

Cox-2, cyclooxygenase-2; IQR, interquartile range; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug.

Table 2. Univariable (Chi-Square and *t* Test for Categorical and Continuous Variables, Respectively) and Multivariable Results by Liposomal Bupivacaine Use in the Peripheral Nerve Block Cohort

	Use of Liposomal Bupivacaine				
	Univariable Results			Multivariable Results	
	Yes (n = 18,817) n (%)	No (n = 70,013) n (%)	*P* Value	Yes (Reference = No) Odds Ratio (95% CI)	*P* Value
Opioid-related complications					
Respiratory complications	199 (1.1)	1,205 (1.7)	< 0.0001	1.08 (0.78, 1.50)	> 0.999
Genitourinary complications	286 (1.5)	1,233 (1.8)	0.0235	1.01 (0.75, 1.35)	> 0.999
Central nervous system complications	117 (0.6)	491 (0.7)	0.2402	1.09 (0.73, 1.63)	> 0.999
Gastrointestinal complications	289 (1.5)	1,671 (2.4)	< 0.0001	0.97 (0.74, 1.29)	> 0.999
Other complications	137 (0.7)	897 (1.3)	< 0.0001	0.83 (0.57, 1.21)	> 0.999
Naloxone use	107 (0.6)	620 (0.9)	< 0.0001	1.01 (0.66, 1.54)	> 0.999
Inpatient opioid prescription					
Total opioids (mg OME)	190 (120–298)	272 (173–413)	< 0.0001	–9.3% (–11.1%, –7.5%)	< 0.0001
Day 0 opioids (mg OME)	98 (60–150)	126 (75–203)	< 0.0001	–7.6% (–9.6%, –5.5%)	< 0.0001
Day 1 opioids (mg OME)	50 (24–87)	60 (30–102)	< 0.0001	–7.4% (–10.0%, –4.8%)	< 0.0001
Day 1+ opioids (mg OME)	30 (0–65)	55 (23–105)	< 0.0001	–7.6% (–10.8%, –4.3%)	< 0.0001
Resource utilization					
Cost of hospitalization (US dollars)	15,013 (13,113–18,088)	15,810 (13,503–19,022)	< 0.0001	2.2% (–0.1%, 4.6%)	0.0900
Length of stay (days)	2 (2–3)	3 (2–3)	< 0.0001	–8.8% (–10.1%, –7.5%)	< 0.0001

Multivariable models were adjusted for age, volume of annual total knee arthroplasties per hospital, hospital size, Charlson–Deyo Index, sex, race, year, insurance, teaching status, hospital area, general anesthesia use, neuraxial anesthesia use, liposomal bupivacaine, nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, ketamine, gabapentinoids, patient-controlled analgesia, intravenous acetaminophen, and the comorbidities for substance use/abuse, pain conditions, and psychiatric conditions. Other complications include postoperative bradycardia, rash or itching, drugs causing adverse effects with therapeutic use, and fall from bed.

OME, oral morphine equivalents.

Furthermore, liposomal bupivacaine use was not associated with significantly lower odds for opioid-related complications in patients undergoing a total knee arthroplasty with a peripheral nerve block. The c-statistics for the associated models varied between 0.75 and 0.79 indicating sufficient model discrimination. The intraclass correlation coefficient demonstrated that 79% of the variability in liposomal bupivacaine use can be accounted for by hospital-level factors.

Sensitivity analyses restricting the cohort to hospitals with more than 50% liposomal bupivacaine use showed similar effect estimates for inpatient opioid prescription and length and cost of hospitalization (tables 3 and 4). Supplemental Digital Content 3 to 6 (http://links.lww.com/ALN/B721, http://links.lww.com/ALN/B722, http://links.lww.com/ALN/B723, http://links.lww.com/ALN/B724) depict the same analyses in two subgroups of patients undergoing total knee arthroplasty with a peripheral nerve block and (1) general anesthesia or (2) neuraxial anesthesia. Multivariable results in these cohorts also showed a nonclinically significant reduction in inpatient opioid prescription associated with the use of liposomal bupivacaine when compared to no liposomal bupivacaine use. However, the effect was more pronounced in the general anesthesia subgroup (–12.3%; CI –14.8%, –9.7%; $P < 0.0001$), whereas in the neuraxial anesthesia subgroup the reduction was not statistically significant (–6.1%; CI –14.6%, 3.2%; $P > 0.999$).

In addition, we performed an analysis to assess whether using the individual Charlson–Deyo comorbidities in our multivariable models would produce different results compared to the use of the Charlson–Deyo index. Liposomal bupivacaine was associated with –9.3% (CI –10.4%, –8.2%) reduction in total inpatient opioid prescription when using a model with individual comorbidities; this was –9.3% (CI –11.1%, –7.5%) when using a model with the Charlson–Deyo index. Because the results are essentially unaltered, we opted to continue using the Charlson–Deyo index in our multivariable models.

Discussion

In this observational study of 88,830 total knee arthroplasties in patients who also received a peripheral nerve block, we were unable to determine an association between liposomal bupivacaine use and clinically meaningful reductions in inpatient opioid prescription. Furthermore, no relevant impact of liposomal bupivacaine use on complications or resource utilization was observed. Our sensitivity analyses supported results from our main analysis, demonstrating the robustness of our results. Although only a minority of patients (21.2%) received liposomal bupivacaine, an initial increase in the utilization of this product was seen over time. Utilization reached a plateau in the latter 2 yr of the study. In addition, we demonstrated substantial interhospital variation in the use of liposomal bupivacaine, which was also reflected in the intraclass correlation coefficient.

Table 3. Patient Demographics, Healthcare-related, Procedure-related, and Comorbidity-related Variables (Chi-Square and *t* Tests for Categorical and Continuous Variables, Respectively) by Liposomal Bupivacaine Use for the Sensitivity Analysis in Hospitals with More than 50% Liposomal Bupivacaine Use

	Use of Liposomal Bupivacaine, n (%)		
	Yes (n = 11,606)	No (n = 4,428)	*P* Value
Patient demographics			
Age (yr), median (IQR)	67 (61–73)	66 (59–73)	< 0.0001
Sex			0.9364
Female	7,187 (61.9)	2,739 (61.9)	
Male	4,419 (38.1)	1,689 (38.1)	
Race/ethnicity			0.0008
White	9,691 (83.5)	3,586 (81.0)	
Black	1,381 (11.9)	603 (13.6)	
Other	534 (4.6)	239 (5.4)	
Comorbidity-related			
Charlson–Deyo comorbidity index (categorized)			0.0002
0	8,608 (74.2)	3,150 (71.1)	
1	2,193 (18.9)	915 (20.7)	
2	560 (4.8)	232 (5.2)	
2+	245 (2.1)	131 (3.0)	
Substance use/abuse	825 (7.1)	393 (8.9)	0.0002
Pain conditions	1,937 (16.7)	696 (15.7)	0.1377
Psychiatric conditions	2,364 (20.4)	926 (20.9)	0.4460
Procedure-related			
Year of procedure			< 0.0001
2013	1,107 (9.5)	1,754 (39.6)	
2014	3,004 (25.9)	890 (20.1)	
2015	3,988 (34.4)	758 (17.1)	
2016	3,507 (30.2)	1,026 (23.2)	
General anesthesia use	7,612 (65.6)	2,812 (63.5)	0.0135
neuraxial anesthesia Use	1,247 (10.7)	507 (11.5)	0.2007
NSAIDs use	6,897 (59.4)	2,426 (54.8)	< 0.0001
Cox-2 inhibitors use	7,195 (62.0)	1,985 (44.8)	< 0.0001
Ketamine use	648 (5.6)	252 (5.7)	0.7910
Gabapentinoids use	6,304 (54.3)	1,949 (44.0)	< 0.0001
IV acetaminophen use	5,729 (49.4)	1,511 (34.1)	< 0.0001
Patient-controlled analgesia use	137 (1.2)	141 (3.2)	< 0.0001
Healthcare-related			
Insurance type			0.0036
Commercial	3,998 (34.4)	1,600 (36.1)	
Medicaid	213 (1.8)	116 (2.6)	
Medicare	7,056 (60.8)	2,593 (58.6)	
Uninsured	17 (0.1)	7 (0.2)	
Unknown	322 (2.8)	112 (2.5)	
Hospital location			0.3114
Rural	344 (3.0)	118 (2.7)	
Urban	11,262 (97.0)	4,310 (97.3)	
Hospital size			< 0.0001
< 300 beds	6,024 (51.9)	2,721 (61.5)	
300–499 beds	5,514 (47.5)	1,687 (38.1)	
≥ 500 beds	68 (0.6)	20 (0.5)	
Hospital teaching status			< 0.0001
Nonteaching	8,038 (69.3)	3,353 (75.7)	
Teaching	3,568 (30.7)	1,075 (24.3)	
Annual total knee arthroplasties per hospital, median (IQR)	485 (331–770)	435 (331–770)	0.1328

Cox-2, cyclooxygenase-2; IQR, interquartile range; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug.

Table 4. Univariable (*t* Test for Comparisons) and Multivariable Results by Liposomal Bupivacaine Use for the Sensitivity Analysis in Hospitals with More than 50% Liposomal Bupivacaine Use

	Use of Liposomal Bupivacaine				
	Univariable Results			Multivariable Results	
	Yes (n = 11,606) Median (IQR)	No (n = 4,428) Median (IQR)	*P* Value	Yes (Reference = No) Percent Change (95% CI)	*P* Value
Inpatient opioid prescription					
Total opioids (mg OME)	170 (110–260)	235 (140–357)	< 0.0001	–12.6% (–16.0%, –9.0%)	< 0.0001
Day 0 opioids (mg OME)	95 (55–138)	113 (60–180)	< 0.0001	–9.4% (–12.9%, –5.7%)	< 0.0001
Day 1 opioids (mg OME)	45 (20–75)	56 (30–90)	< 0.0001	–7.7% (–12.5%, –2.6%)	< 0.0001
Day 1+ opioids (mg OME)	23 (0–60)	45 (15–90)	< 0.0001	–9.5% (–15.7%, –2.9%)	< 0.0001
Resource utilization					
Cost of hospitalization (US dollars)	14,356 (12,818–16,572)	14,081 (12,781–16,271)	0.0002	–3.1% (–10.6%, 5.0%)	> 0.999
Length of stay (days)	2 (2–3)	2 (2–3)	< 0.0001	–13.1% (–15.9%, –10.3%)	< 0.0001

Multivariable models were adjusted for age, volume of annual total knee arthroplasties per hospital, hospital size, Charlson–Deyo Index, sex, race, year, insurance, teaching status, hospital area, general anesthesia use, neuraxial anesthesia use, liposomal bupivacaine, nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, ketamine, gabapentinoids, patient-controlled analgesia, intravenous acetaminophen, and the comorbidities for substance use/abuse, pain conditions, and psychiatric conditions.

IQR, interquartile range; OME, oral morphine equivalents.

The reasons for the variability in liposomal bupivacaine use have to remain speculative but are likely to include physician and patient preference. We have previously shown that pain management modalities vary widely among hospitals.[39] Factors influencing the choice to use a certain medication may be institution- and provider-related. They may include differences in experience and training, the use of protocols and cost considerations.[40] Although the rapid increase in its utilization in the first 3 yr on the market can be attributed to the fact that liposomal bupivacaine is a new drug, approved by the Food and Drug Administration in 2011, this trend may also reflect the growing awareness for opioid-related adverse effects and the desire to reduce them.[41,42] A more recent reduction, however, is noteworthy, and although no firm conclusions can be drawn from our data, this finding may at least in part be explained by the lack of data supporting its efficacy in this patient population in the context of its relatively high cost.

We did not observe a clinically meaningful reduction in inpatient opioid prescription and resource utilization outcomes. Moreover, liposomal bupivacaine use was not associated with any difference in opioid-related complications. This suggests that in the context of state-of-the-art pain management including peripheral nerve blocks, liposomal bupivacaine may have a limited role. This is in line with a recent publication by Amundson *et al.*,[10] suggesting that liposomal bupivacaine is inferior to the use of femoral catheters plus sciatic blocks in total knee arthroplasties. The authors of this study also found that liposomal bupivacaine was not superior to a ropivacaine mixture.

Bagsby *et al.*[14] also demonstrated that a periarticular liposomal bupivacaine injection in primary total knee arthroplasty patients had no benefit over ropivacaine regarding pain and opioid usage. The authors concluded that when a multimodal pain protocol is being used, liposomal bupivacaine does not beneficially influence pain control. Similar results have been reported by Schroer *et al.*[13] In their prospective, blinded, randomized study of 111 patients undergoing a total knee arthroplasty and receiving a multimodal pain therapy, they found no benefit of liposomal bupivacaine over bupivacaine.

On the other hand, there is a variety of studies that suggest a positive effect of liposomal bupivacaine in total knee arthroplasty. However, some of those studies do not include comparable control groups. In a recent publication, Mont *et al.*[43] concluded that local infiltration of liposomal bupivacaine improves pain scores and opioid use after total knee arthroplasty. However, because the control group received significantly lower amounts of local anesthetics (100 mg of bupivacaine in the control group *vs.* 100 mg of bupivacaine plus 266 mg of liposomal bupivacaine in the study group), it does not seem surprising that the study group had better outcomes. Next to questionable control groups, currently published studies do not address the fact that potential efficacy of liposomal bupivacaine in highly selective trials may not translate to effectiveness in real-world settings. Indeed, while focusing on its safety profile, liposomal bupivacaine gained Food and Drug Administration acceptance based on trials performed in patients undergoing bunionectomies and hemorrhoidectomies,[44,45] a far cry from its widespread utilization in much larger surgeries characterized by more pain and opioid utilization.

Interestingly, we found that in those patients within the peripheral nerve block cohort that received general anesthesia, liposomal bupivacaine was associated with a more pronounced reduction in inpatient opioid prescription compared to those that received neuraxial anesthesia. Although this may be due to the higher baseline opioid utilization (as demonstrated by the higher inpatient opioid prescription) in this cohort, this further questions the value of liposomal

bupivacaine in light of real-world practices where state-of-the-art anesthetic and pain management is used, including peripheral nerve blocks and neuraxial anesthesia/analgesia.

Our study is subject to a number of limitations. Because of the retrospective design, we can only determine associations and not causal relationships. Therefore, associations have to be interpreted taking into account plausibility. Furthermore, the Premier Healthcare data were collected for administrative and not for research purposes, thus resulting in a lack of clinical details such as pain scores and clinical conditions only captured if they are billed for. Therefore, as residual confounding may exist, it is prudent to perform sensitivity analyses to assess robustness of results, which we confirmed in the current study. The definition of comorbidities and complications is based on the ICD-9 coding system and may be burdened with coding bias. This can lead to underestimation of adverse events, but again it is likely to affect patients from different groups (those with and without liposomal bupivacaine) equally. In addition, administrative data provide information only on billing for medication and not actual administration/consumption. This may include cases where one whole vial was billed, but only a portion administered with the rest discarded. Although it is likely that some level of association between billing and use of opioids exists, the utilization of multimodal analgesia may be associated with a propensity to prescribe less opioids. Thus, prescribers and users of liposomal bupivacaine or other nonopioids may be biased to order/dispense less opioid derivatives than those who do not. Furthermore, it is important to point out the difference between statistical significance and clinical meaningfulness in large database studies. To reflect this, we used a 15% threshold for clinical importance. Because the placebo effect is often estimated as a 20 to 30% clinical effect, our lower threshold would be considered more liberal by many readers. However, because most patients would not be aware of liposomal bupivacaine administration, we expect a limited placebo effect. Moreover, use of a higher threshold could be interpreted as biased toward our hypothesis that liposomal bupivacaine does not improve outcomes, mainly in respect to pain and opioid utilization. These issues will be resolved when more data are available on specifically the minimum reduction in opioid utilization needed to result in reduced risk for adverse effects, a current gap in the literature. Another limitation is that the Premier database does not provide information on preoperative opioid use, which might be a confounder and ideally should be included as a covariate. However, we adjusted for substance use/abuse, chronic pain conditions, and psychiatric conditions, which can be associated with preoperative opioid use. Indeed, previous studies have shown that around 20% of patients undergoing total knee arthroplasty use opioids preoperatively, which is in line with the prevalence of chronic pain in the current study (for which we adjust).[46,47] Finally, using the Premier database, we were not able to differentiate between various routes of administration of liposomal bupivacaine. Although we expect most use to be in line with liposomal bupivacaine's Food and Drug Administration approval (infiltration at the surgical site), off-label use of liposomal bupivacaine (*e.g.*, in a peripheral nerve block) is possible in some cases included in this study. This would entail that the effects demonstrated in our study are an average effect of routes of administration included in our cohort. Under the assumption that most use will be in line with the Food and Drug Administration approval, any other route of administration will need to exert substantial effects to affect the mean effect in our cohort. Although more detailed studies are needed on differential effectiveness of liposomal bupivacaine by route of administration, this assumption suggests that the effect of liposomal bupivacaine may be limited, especially in light of current state of the art pain management approaches including peripheral nerve and neuraxial blocks.

In conclusion, we failed to show a clinically meaningful reduction in either inpatient opioid prescription, opioid-related complications, or resource utilization outcomes among patients receiving liposomal bupivacaine as part of their total knee arthroplasty. Given the number of recent publications that suggest a lack of benefit of the addition of liposomal bupivacaine to a multimodal regimen including a regional analgesic technique, its routine use should be carefully examined, especially given its relatively high cost. Future studies will need to evaluate the effectiveness of liposomal bupivacaine separately for the different routes of administration.

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Competing Interests

Dr. Memtsoudis is a director on the boards of the American Society of Regional Anesthesia and Pain Medicine, Pittsburgh, Pennsylvania, and the Society of Anesthesia and Sleep Medicine, Milwaukee, Wisconsin. He is a one-time consultant for Sandoz Inc., Princeton, New Jersey, and the holder of U.S. Patent US-2017-0361063, Multicatheter Infusion System. He is the owner of SGM Consulting, LLC, Rumson, New Jersey, and co-owner of FC Monmouth, LLC, Fairhaven, New Jersey. None of the above relations influenced the conduct of the present study. The other authors declare no competing interests.

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