A Cost-Minimization Analysis Evaluating the Use of Liposomal Bupivacaine in Reconstructive Plastic Surgery Procedures

Andrea Little, M.D., M.B.A.
Kristin Brower, Pharm.D., B.C.P.S.
Deborah Keller, M.D.
Bruce Ramshaw, M.D.
Jeffrey E. Janis, M.D.

Grand Rapids, Mich.; Columbus, Ohio; Dallas, Texas; and Knoxville, Tenn.

Background: Postsurgical pain management is critical to patient satisfaction and value. Several studies have evaluated liposomal bupivacaine in postoperative pain management protocols; however, its economic feasibility remains undefined. This study analyzes the economic impact of liposomal bupivacaine using a national claims database to assess postoperative clinical and financial outcomes in plastic and reconstructive procedures.

Methods: The Vizient Clinical Data Base/Resource Manager electronic database was reviewed for plastic surgery procedures (i.e., abdominoplasty, abdominal wall reconstruction, mastectomy with immediate tissue expander placement, mastectomy with direct-to-implant reconstruction, autologous breast reconstruction, and augmentation mammaplasty) at participating hospitals from July 1, 2016, to July 1, 2017. The main outcome measures were the length of stay; 7-, 14-, and 30-day readmission rates; and direct and total costs observed.

Results: During the study period, 958 total cases met inclusion criteria. Liposomal bupivacaine was used in 239 cases (25 percent). Compared with cases that did not use liposomal bupivacaine, liposomal bupivacaine cases had a decreased length of stay (9.2 days versus 5.8 days), decreased cost (total cost, $39,531 versus $28,021; direct cost, $23,960 versus $17,561), and lower 30-day readmission rates (4 percent versus 0 percent). The 14- and 7-day readmission rates were similar between the two groups.

Conclusions: The use of liposomal bupivacaine may contribute to a reduction in length of stay, hospital costs, and 30-day readmission rates for abdominal and breast reconstructive procedures, which could contribute to a favorable economic profile from a system view. Focusing on the measurement and improvement of value in the context of whole, definable, patient processes will be important as we transition to value-based payments. (*Plast. Reconstr. Surg.* 143: 1269, 2019.)

The United States is amidst an opioid epidemic, and the president has directed the Department of Health and Human Services to declare the opioid crisis a public health emergency. According to the Centers for Disease Control and Prevention, adverse events and deaths from prescription opioids have more than quadrupled since 1999.[1] Although opioids are a cornerstone in management of acute pain in the short term, the development of effective, opioid-sparing perioperative modalities for reduction of postoperative pain has become increasingly relevant. More than 80 percent of patients who

From the Plastic and Reconstructive Residency Program, Michigan State University College of Human Medicine Spectrum Health; the Departments of Anesthesiology and Plastic Surgery, The Ohio State University Wexner Medical Center; the Division of Colon and Rectal Surgery, Department of Surgery, Baylor University Medical Center; and the Department of Surgery, University of Tennessee Graduate School of Medicine.
Received for publication March 11, 2018; accepted August 29, 2018.

DOI: 10.1097/PRS.0000000000005435

Disclosure: *Dr. Janis has served a prior consultant for Pacira Pharmaceuticals, LifeCell, Bard, Daiichi Sankyo, and Allergan, ending in October 2017. He receives royalties from Thieme Publishing. Drs. Janis, Keller, and Ramshaw have received consulting fees and speaker fees from Pacira Pharmaceuticals, which produces and sells liposomal bupivacaine (Exparel). Drs. Little and Brower have no financial information to disclose. No funding was received for this article.*

undergo surgical procedures continue to experience moderate to severe postoperative pain.[2] Inadequate pain control results in increased levels of anxiety, guarded breathing, delayed recovery, and decreased wound healing.[3] Significant physiologic and economic consequences of uncontrolled pain include opioid-related adverse events such as sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression; increased length of hospital stay; increased hospital costs; and poor patient satisfaction.[4] Alternatively, adequate postoperative analgesia has been shown to decrease thrombus formation; expedite recovery; and improve respiratory, cardiovascular, and gastrointestinal function.[5]

Local anesthetics can potentially help reduce the burden caused by opioid-related adverse events. Long-acting anesthetics such as bupivacaine hydrochloride have the benefit of a prolonged duration of action (8 to 12 hours) and can be delivered by means of a single bolus injection or a continuous infusion. Bolus injections have minimal effect on postsurgical pain. Continuous infusion of long-acting bupivacaine has shown some success in amelioration of postoperative pain but can be cumbersome to both the patient and the health care team, as it requires placement and maintenance of perineural catheters, additional training and skills of tertiary care providers, and medical literacy and understanding on behalf of the patient. In addition, its use is associated with increased costs and higher rates of complications.[6] Liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, Inc., Parsippany, N.J.) was developed to address these issues with an extended-release formulation. Liposomal bupivacaine is delivered in situ by means of a biocompatible and biodegradable multivesicular lipid-based vehicle that encapsulates the drug within aqueous pores and allows diffusion over a prolonged period.[6] As the three-dimensional lipid membranes erode from outer layer to inner layers, bupivacaine is released over time, with an initial peak at 0.25 to 2 hours and a second peak at 12 to 24 hours after injection, and with duration of relief lasting 48 to 72 hours.[7] Its efficacy has been demonstrated across surgical service lines, including bariatric, colorectal, general, gynecologic, urologic, orthopedic, and reconstructive procedures.[7–18] Debate remains, however, regarding the value of liposomal bupivacaine's use considering the high initial cost of the drug compared with its alternatives (liposomal bupivacaine, $315 per 366-mg/20-ml vial; bupivacaine hydrochloride, $5.24 per 75 ml).[9,19]

PATIENTS AND METHODS

A retrospective claims analysis was performed using the Vizient Clinical Data Base/Resource Manager (Vizient, Inc., Irving, Texas) abstract discharge database (data from the Vizient Clinical Data Base/Resource Manager used by permission of Vizient. All rights reserved[20]) to identify abdominal wall and breast reconstructive procedures at participating hospitals from July 1, 2016, to July 1, 2017. Vizient, Inc., is the largest health care performance improvement company in the United States. The contents of the Vizient Clinical Data Base/Resource Manager includes demographic and encounter characteristics for patients receiving care at 140 academic medical centers and 210 other community hospitals.

All patients who underwent abdominal wall and breast reconstructive procedures with *International Classification of Diseases, Tenth Revision*, codes listed in Table 1 were included in the analysis. Expected values were calculated using the 2016 (academic medical centers) base-Medical Service Diagnosis-Related Group risk models. The data were all provided as aggregate data from 54 various institutions across the United States.

The main outcome measures were the length of stay; 7-, 14-, and 30-day readmission rates; and direct and total costs observed for the liposomal bupivacaine group compared to expected values. Total costs were defined as all costs (both direct and indirect costs) associated with the care of the patient, including institutional operating, staffing, and all other costs assigned to the patient. Direct costs were defined as all costs accumulated that related to the direct care of the patient (e.g., surgical supplies, medications).

For statistical analysis, univariate analysis was performed using Stata v5.0 (StataCorp, College Station, Texas) on all variables using a one-way analysis of variance of transformed variables with weighting to account for the different number of cases at each institution. The number of observations refers to the number of institutions, and the frequency refers to the total number of subjects at the institutions in the liposomal bupivacaine or non–liposomal bupivacaine groups. Data for length of stay and cost were given as the mean with standard deviation. Because of the nonnormality of the readmission rates, those data are reported as the medians. Readmission rates were transformed using the inverse hyperbolic sine

Table 1. *International Classification of Diseases, Tenth Revision*, Codes

Procedure	Code
Abdominoplasty	
Open alteration of abdominal wall (no tissue substitute)	0W0F0ZZ
Open repair of abdominal wall	0WQF0ZZ
Abdominal wall reconstruction	
Open reconstruction by supplementing synthetic tissue	0JU80JZ
Open reconstruction by supplementing autologous tissue substitute	0JU807Z
Mastectomy with immediate breast reconstruction	
Mastectomy right breast; insertion tissue expander right	0HTT0ZZ
Mastectomy left breast; insertion tissue expander left	0HTU0ZZ
Mastectomy right both breast; insertion tissue expander both breasts	0HTV0ZZ
Mastectomy with direct-to-implant breast reconstruction	
Mastectomy right breast with saline/silicone implant insertion	0HRT0JZ
Mastectomy left breast with saline/silicone implant insertion	0HRU0JZ
Mastectomy both breasts with saline/silicone implant insertion	0HRV0JZ
Augmented mammaplasty	
Open alteration right breast with synthetic tissue substitute	0H0T0JZ
Open alteration left breast with synthetic tissue substitute	0H0U0JZ
Open alteration both breasts with synthetic tissue substitute	0H0V0JZ
Autologous breast reconstruction	
Right breast reconstruction with latissimus dorsi free muscle flap	0HRT075
Left breast reconstruction with latissimus dorsi free muscle flap	0HRU075
Bilateral breast reconstruction with latissimus dorsi free muscle flap	0HRV075
Right breast reconstruction with TRAM flap	0HRT076
Left breast reconstruction with TRAM flap	0HRU076
Bilateral breast reconstruction with TRAM flap	0HRV076

TRAM, transverse rectus abdominis musculocutaneous.

transformation before the analysis. Statistical significance was defined at an alpha level less than 0.05.

RESULTS

During the study period, there were 958 total cases that met inclusion criteria. Liposomal bupivacaine was used in 239 of these cases (25 percent). The analysis shown in Tables 2 through 4 found a lower mean length of stay (5.8 days versus 9.2 days; $p = 0.004$), lower mean total and direct costs (total cost $28,021 versus $39,531, $p = 0.020$; direct cost, $17,561 versus $23,960, $p = 0.047$), and lower 30-day readmission rates (0 percent versus 4 percent; $p = 0.043$) for the liposomal bupivacaine versus control groups. The 14- and 7-day readmission rates were not significantly different between the two groups (14-day readmission rates, 3 percent versus 0 percent, $p = 0.116$; 7-day readmission rates, 2 percent versus 0 percent, $p = 0.490$).

DISCUSSION

Cost-effectiveness of long-acting local anesthetics is a topic of particular interest in the current health care landscape. In the face of the national opioid epidemic and rising health care costs, this is of critical importance to all stakeholders—patients, providers, and institutions alike. For the past decade in health care, the United States has witnessed a growing acceptance of the need to

Table 2. Length of Stay

	LB				Control				
	No. of Obs.	Frq	Mean	SD	No. of Obs.	Frq	Mean	SD	*p*
LOS (days)	53	1663	5.8	2.9	285	31,369	9.2	4.8	0.004

LB, liposomal bupivacaine; LOS, length of stay; Obs, observations; Frq, frequency.

Table 3. Direct and Total Costs

	LB				Control				
	No. of Obs.	Frq	Mean	SD	No. of Obs.	Frq	Mean	SD	*p*
Direct cost	49	1510	$17,561	$9910	241	28,264	$23,960	$12,053	0.047
Total cost	49	1510	$28,021	$14,636	241	28,264	$39,531	$18,512	0.020

LB, liposomal bupivacaine; Obs, observations; Frq, frequency.

Table 4. Readmission Rates

Readmission Rate	LB				Control				
	No. of Obs.	Frq	Median (%)	Range	No. of Obs.	Frq	Median (%)	Range	*p*
30 days	53	1541	0	0–33	285	28,317	4	0–25	0.043
14 days	53	1541	0	0–33	285	28,317	3	0–25	0.116
7 days	53	1541	0	0–33	285	28,317	2	0–25	0.490

LB, liposomal bupivacaine; Obs, observations; Frq, frequency.

transition from a disconnected system that is reimbursed based on volume or revenue growth to one that is based on measuring and improving value for patients and those who care for them. As we transition to a value-based payment system, these benefits will be increasingly important to improve the value of care we provide for patients.

At first glance, liposomal bupivacaine appears significantly more expensive than bupivacaine hydrochloride.[9,19] It is important, however, to consider the links between reduced narcotic use, decreased complications, and decreased length of hospital stay, all of which contribute to overall reduction of health care costs. Earlier return to function, quicker ambulation, improved healing, and prevention of chronic pain also lessen the economic burden and can lead to increased patient satisfaction. Initial concerns that reduced length of hospital stays would result in increased hospital readmissions have been consistently disproven.[10]

As to continuous infusions, Hollander et al. compared the use of liposomal bupivacaine and subfascial continuous anesthesia with catheter-directed continuous infusion by means of an elastomeric pump and traditional morphine patient-controlled analgesia. Operating time was longer for subfascial continuous anesthesia compared to liposomal bupivacaine (219.8 minutes versus 199.3 minutes; $p < 0.01$). In addition to extra costs associated with longer operating times, the price of liposomal bupivacaine was $285 versus $460 for the catheter-directed infusion device plus $400 for the ropivacaine infusion.[11]

A comparative analysis performed at a large hospital system reviewed five perioperative pain modalities, including the following: (1) continuous femoral nerve blocks, (2) indwelling epidural anesthesia, (3) elastomeric pumps, (4) single-shot femoral/sciatic nerve blocks, and (5) liposomal bupivacaine. Liposomal bupivacaine resulted in reduced morphine equivalent opioid consumption (130.2 mg versus 110.4 mg; $p = 0.0035$) and decreased cost per episode of care (range, $130.29 to $702.14) compared to continuous or single-shot nerve block and elastomeric pumps. Only indwelling epidural catheters (12 hour epidural and ropivacaine drip) resulted in lower cost per episode ($169 to $192).[12]

In a prospective, phase IV sequential cohort studies assessing health economic outcomes, Candiotti et al. showed mean hospital costs of $11,234 in the liposomal bupivacaine–based multimodal analgesia group compared to $13,018 in the standard intravenous opioid patient-controlled analgesia group ($p = 0.2612$).[13] In patients undergoing ileostomy reversal, hospital costs averaged $6482 versus $9282 ($p = 0.01$) in patients treated with liposomal bupivacaine compared with patient-controlled analgesia.[14] Alternatively, Nadeau et al. studied the use of bupivacaine versus liposomal bupivacaine in augmentation mammaplasty and failed to find an appreciable clinical benefit that justified the additional cost of liposomal bupivacaine.[21] In this study, 100-mg of non–liposomal bupivacaine was instilled into one breast pocket and 130 mg of liposomal bupivacaine was injected into the contralateral breast pocket before closure in 34 patients undergoing augmentation mammaplasty. Although the data demonstrated mild improvement in postoperative pain in the liposomal bupivacaine side compared to the non–liposomal bupivacaine side, 70 percent of the patients did not feel the reduction in pain on the liposomal bupivacaine side enough to justify a $250 increase in cost in this cosmetic cohort. It is important to note that although dosing equivalency has not been formally established, other studies have shown that the maximum plasma bupivacaine concentration produced by bupivacaine hydrochloride 100 mg is similar to that produced by liposomal bupivacaine 266 mg.[15] The majority of studies that have documented success with liposomal bupivacaine have obtained significant results using 266 mg (the recommended maximum dose). Therefore, 130 mg of liposomal bupivacaine may have been a subtherapeutic dose in this particular study.

The use of liposomal bupivacaine has been studied across various surgical specialties including colorectal, bariatric, urologic, orthopedic, and reconstructive procedures. Used in conjunction with a multimodal analgesia protocol,

liposomal bupivacaine has been particularly effective in reducing physiologic stress to facilitate an early recovery. Several institutions have incorporated liposomal bupivacaine effectively into their enhanced recovery after surgery protocols, including in plastic surgery procedures, including, but not limited to, augmentation mammaplasty, immediate breast reconstruction and abdominal wall reconstruction.[16]

We have previously analyzed the efficacy of liposomal bupivacaine as part of a multimodal analgesia regimen in abdominal wall reconstruction. Liposomal bupivacaine was injected in three different planes: directly around the intercostal nerves after performing retrorectus dissection, in the subdermal plane around the incision, and in the transversus abdominis plane. We found decreased postoperative narcotic requirements.[18,22–24]

There are studies where the benefits of liposomal bupivacaine have not been demonstrated or have been minimal, making it difficult to justify the increased costs compared with less expensive alternatives.[25–27] Some potential explanations for these results include the possibility that liposomal bupivacaine may not work as well in some patient subpopulations, for example, patients who are already taking opioids preoperatively.[27] It is also possible that the quality of the infiltration technique impacted the effectiveness of liposomal bupivacaine in some studies. One study demonstrated that the quality of the infiltration technique can impact outcomes.[28]

We recognize the limitation of this work. Observations of this review derive from data submitted by academic medical centers to a national claims database system. As such, length of stay, costs, and readmission rates may differ for nonacademic centers. Because of the database limitation to in-hospital events, the true incidence of complications may be underestimated. The greatest limitation of this review is the potential for coding bias and the reliance on administrative classification *International Classification of Diseases, Tenth Revision*, and CPT codes, which assume concordance between coding technicians and treating providers. Another limitation is the possibility that the surgeons who have used liposomal bupivacaine are doing so in the context of multimodal pain management and enhanced recovery programs that improve outcomes as a result of multiple factors in addition to the use of liposomal bupivacaine. It is possible that surgeons who have not used liposomal bupivacaine are also not implementing other components of multimodal pain management and enhanced recovery programs.

CONCLUSIONS

In this claims analysis, liposomal bupivacaine was associated with improved financial and postoperative clinical outcomes in abdominal wall and breast reconstructive procedures. The use of liposomal bupivacaine may contribute to a reduction in length of stay, overall hospital costs, and readmission rates for abdominal wall and breast reconstructive procedures, which could contribute to improving value from a system view. Focusing on the measurement and improvement of value in the context of whole, definable patient processes will be important as we transition to value-based payments.

Jeffrey E. Janis, M.D.
Department of Plastic Surgery
The Ohio State University Wexner Medical Center
915 Olentangy River Road
Columbus, Ohio 43212
jeffrey.janis@osumc.edu
Twitter: @jjanismd

REFERENCES

1. Centers for Disease Control and Prevention. Wide-ranging online data for epidemiologic research (WONDER). Available at: http://wonder.cdc.gov. Accessed August 4, 2017.
2. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016;17:131–157.
3. McGuire L, Heffner K, Glaser R, et al. Pain and wound healing in surgical patients. *Ann Behav Med.* 2006;31:165–172.
4. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008;11(Suppl):S105–S120.
5. Saraghi M, Hersh EV. Three newly approved analgesics: An update. *Anesth Prog.* 2013;60:178–187.
6. Chahar P, Cummings KC III. Liposomal bupivacaine: A review of a new bupivacaine formulation. *J Pain Res.* 2012;5:257–264.
7. Bergese SD, Onel E, Portillo J. Evaluation of DepoFoam bupivacaine for the treatment of postsurgical pain. *Pain Manag.* 2011;1:539–547.
8. Gan TJ, Robinson SB, Oderda GM, Scranton R, Pepin J, Ramamoorthy S. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. *Curr Med Res Opin.* 2015;31:677–686.
9. Premkumar A, Samady H, Slone H, Hash R, Karas S, Xerogeanes J. Liposomal bupivacaine for pain control after anterior cruciate ligament reconstruction: A prospective, double-blinded, randomized, positive-controlled trial. *Am J Sports Med.* 2016;44:1680–1686.
10. Fayezizadeh M, Petro CC, Rosen MJ, Novitsky YW. Enhanced recovery after surgery pathway for abdominal wall reconstruction: Pilot study and preliminary outcomes. *Plast Reconstr Surg.* 2014;134(Suppl 2):151S–159S.
11. Hollander AB, Scovell JM, Mercado MA, et al. Perioperative injection of liposomal bupivacaine reduces narcotic medication requirement after laparoendoscopic single site donor nephrectomy with shorter operating time than sub-fascial continuous local anesthesia. *J Urol.* 2014;191(Suppl 4S):e-828–e-829.

12. Springer B, Bear S, Christian E. Thinking beyond hospital pharmacy silo analysis of pain modalities in total joint arthroplasty. Paper presented at: Annual Meeting of the American Academy of Orthopaedic Surgeons; March 24–28, 2015; Las Vegas, Nev.
13. Candiotti K, Sands LR, Lee E, et al. Liposomal bupivacaine for postsurgical analgesia in adult patients undergoing laparoscopic colectomy: Results from prospective phase IV sequential cohort studies assessing health economic outcomes. *Curr Ther Res Clin Exp.* 2013;76:1–6.
14. Marcet JE, Nfonsam VN, Larach S. An extended paIn relief trial utilizing the infiltration of a long-acting Multivesicular liPosome foRmulation Of bupiVacaine, EXPAREL (IMPROVE): A phase IV health economic trial in adult patients undergoing ileostomy reversal. *J Pain Res.* 2013;6:549–555.
15. Gasanova I, Alexander J, Ogunnaike B, et al. Transversus abdominis plane block versus surgical site infiltration for pain management after open total abdominal hysterectomy. *Anesth Analg.* 2015;121:1383–1388.
16. 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.
17. Morales R Jr, Mentz H III, Newall G, Patronella C, Masters O III. Use of abdominal field block injections with liposomal bupivacaine to control postoperative pain after abdominoplasty. *Aesthet Surg J.* 2013;33:1148–1153.
18. Butz DR, Shenaq DS, Rundell VL, et al. Postoperative pain and length of stay lowered by use of Exparel in immediate, implant-based breast reconstruction. *Plast Reconstr Surg Glob Open* 2015;3:e391.
19. Micromedex 1.0 (Healthcare Series) (electronic version). Available at: http://www.micromedexsolutions.com. Accessed August 4, 2017.
20. Vizient, Inc. Vizient Clinical Data Base/Resource Manager. Irving, Texas: Vizient; 2016. Available at: https://www.vizientinc.com. Accessed August 4, 2017.
21. Nadeau MH, Saraswat A, Vasko A, Elliott JO, Vasko SD. Bupivacaine versus liposomal bupivacaine for postoperative pain control after augmentation mammaplasty: A prospective, randomized, double-blind trial. *Aesthet Surg J.* 2016;36:NP47–NP52.
22. Khansa I, Koogler A, Richards J, Bryant R, Janis JE. Pain management in abdominal wall reconstruction. *Plast Reconstr Surg Glob Open* 2017;5:e1400.
23. Joshi GP, Janis JE, Haas EM, Ramshaw BJ, Nihira MA, Dunkin BJ. Surgical site infiltration for abdominal surgery: A novel neuroanatomical-based approach. *Plast Reconstr Surg Glob Open* 2016;4:e1181.
24. Khansa I, Janis JE. Abdominal wall reconstruction using retrorectus self-adhering mesh: A novel approach. *Plast Reconstr Surg Glob Open* 2016;4:e1145.
25. White S, Vaughan C, Raiff D, Eward W, Bolognesi M. Impact of liposomal bupivacaine administration on postoperative pain in patients undergoing total knee replacement. *Pharmacotherapy* 2015;35:477–481.
26. Beachler JA, Kopolovich DM, Tubb CC, Sayeed SA. Liposomal bupivacaine in total hip arthroplasty: Do the results justify the cost? *J Orthop.* 2017;14:161–165.
27. Schwarzkopf R, Drexler M, Ma MW, et al. Is there a benefit for liposomal bupivacaine compared to a traditional periarticular injection in total knee arthroplasty patients with a history of chronic opioid use? *J Arthroplasty* 2016;31:1702–1705.
28. Khlopas A, Elmallah RK, Chughtai M, et al. The learning curve associated with the administration of intra-articular liposomal bupivacaine for total knee arthroplasty: A pilot study. *Surg Technol Int.* 2017;30:314–320.