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Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial

Michael A. Mont, MD [a, *], Walter B. Beaver, MD [b], Stanley H. Dysart, MD [c], John W. Barrington, MD [d], Daniel J. Del Gaizo, MD [e]

[a] Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, Ohio
[b] Department of Orthopaedic Surgery, OrthoCarolina Hip & Knee Center, Charlotte, North Carolina
[c] Department of Orthopaedic Surgery, Pinnacle Orthopedics, Marietta, Georgia
[d] Department of Orthopaedic Surgery, Joint Replacement Center of Texas, Baylor Medical Center Frisco, Plano, Texas
[e] Department of Orthopaedic Surgery, University of North Carolina Hospitals, Chapel Hill, North Carolina

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ABSTRACT

Background: Local infiltration analgesia (LIA) with liposomal bupivacaine (LB) in patients undergoing total knee arthroplasty (TKA) has yielded mixed results. The PILLAR study, which was designed to minimize limitations associated with previous studies, compared the effects of LIA with or without LB on pain scores, opioid consumption, including proportion of opioid-free patients, time to first opioid rescue, and safety after primary unilateral TKA.

Methods: Patients ($N = 140$) were randomized to LIA with LB 266 mg/20 mL (admixed with bupivacaine HCl 0.5%, 20 mL) or LIA with bupivacaine HCl 0.5%, 20 mL. Standardized infiltration techniques and a standardized multimodal pain management protocol were used. The coprimary efficacy endpoints were area under the curve (AUC) of visual analog scale pain intensity scores 12-48 hours ($AUC_{12\text{-}48}$) postsurgery and total opioid consumption 0-48 hours postsurgery.

Results: Mean $AUC_{12\text{-}48}$ of visual analog scale pain intensity score was 180.8 with LB and 209.3 without LB (least squares [LS] mean treatment difference −26.88, $P = .0381$). LS mean total opioid consumption 0-48 hours postsurgery was 18.7 mg with and 84.9 mg without LB (LS ratio 0.220, $P = .0048$). Significant differences in favor of LB were observed for the percentage of opioid-free patients ($P < .01$) and time to first opioid rescue ($P = .0230$). Treatments were similarly well tolerated.

Conclusion: This study provides data on LIA with LB administered using optimal techniques specific to TKA. In this setting, LIA with LB significantly improved postsurgical pain, opioid consumption, and time to first opioid rescue, with more opioid-free patients and no unexpected safety concerns.

Managing postsurgical pain after total knee arthroplasty (TKA) is challenging but critical to successful surgical outcomes, including patient recovery and rehabilitation [1,2] and overall satisfaction [1,3]. Clinical practice guidelines recommend multimodal therapy combining preoperative, intraoperative, and postoperative medications, including opioids, nonsteroidal anti-inflammatory drugs, gabapentin, pregabalin, and local anesthetics [4,5]. Local infiltration analgesia (LIA) with anesthetic agents has been demonstrated to improve pain control and reduce morphine consumption [6,7]. It also shortens lengths of hospital stays compared with peripheral nerve block [7], which is known to be associated with poor mobility [2].

Liposomal bupivacaine (LB; EXPAREL, bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc., Parsippany, NJ) is an amide local anesthetic approved for single-dose infiltration into the surgical site to produce postsurgical analgesia [8]. Numerous

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* Reprint requests: Michael A. Mont, MD, Department of Orthopaedic Surgery, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195.

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studies have evaluated LIA with LB in patients undergoing TKA, some demonstrating a benefit [9–11] and others not [12–19]. Barrington et al [9], for example, reported that periarticular injection of LB provided better pain control at 6 and 12 hours after TKA compared with periarticular injection of ropivacaine. In contrast, Schroer et al [19] found no differences in postsurgical pain with periarticular injection of LB vs bupivacaine. When attempting to reconcile the conflicting findings in the literature, a variety of differences in study design and methodology are apparent, including differences in infiltration techniques, opioid use, and pain assessments, all of which may have contributed to the disparate results.

The conflicting findings reported in the literature and the need for data obtained using optimal infiltration techniques led us to initiate the PILLAR study [20]. The objectives of the PILLAR study are to compare the effects of LIA, with or without LB, on pain scores, opioid consumption, including proportion of opioid-free patients, time to first opioid rescue, and safety after primary unilateral TKA. To minimize the limitations that may have affected previous study results, including inadequate infiltration volume and technique, lack of opioid minimization in the postsurgical pain management protocol, suboptimal pain assessments, and attrition due to curtailed hospital stay, we used a standardized infiltration protocol alongside an opioid-sparing multimodal pain management protocol and robust analytical methods.

Methods

Methods for the PILLAR study (NCT02713490) were previously published in detail [20]. This phase 4, randomized, double-blind, active-controlled, parallel-group study was conducted at 16 US centers between April 25, 2016, and January 19, 2017. Institutional review boards at each site approved the study protocol, and the study was conducted in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice [21]. All patients provided written consent before participation. Patients were adult men and nonpregnant women who were scheduled to undergo primary, unilateral, tricompartmental TKA under spinal anesthesia, had a primary TKA indication of degenerative knee osteoarthritis, and had an American Society of Anesthesiologists physical status classification of 1, 2, or 3.

Randomization (1:1) was performed via a centralized system to LIA with LB 266 mg/20 mL admixed with bupivacaine HCl 0.5%, 20 mL or LIA with bupivacaine HCl 0.5%, 20 mL only, each expanded with saline to a total volume of 120 mL. Study drug was administered before and after cementation using six 20-mL syringes with 22-gauge needles, each stick delivering approximately 1-1.5 mL to the intended area to achieve visible tissue expansion with minimal leakage. Injection sites were selected based on the areas of highest nerve density. A visual representation of the injection sites is shown in Figure 1. All investigators were required to watch a Video demonstrating the infiltration techniques and to receive training by a medical representative from the study sponsor (Pacira Pharmaceuticals, Inc.). Note, the dosage in the video differs from that discussed in this article (Appendix A). Competency in the standardized approach was confirmed with a quiz and intraoperative observation by the study sponsor (minimum of 3-5 cases for experienced investigators; otherwise, at the sponsor's discretion); all surgeons were deemed competent. Study drug was prepared and administered by unblinded personnel uninvolved with the study assessments.

All patients received acetaminophen 1000 mg, celecoxib 200 mg, oral pregabalin 300 mg, and intravenous (IV) tranexamic acid 1 g within 4 hours before surgery. Intraoperative medication was limited to fentanyl or its analogs. Other analgesics were prohibited intraoperatively except for emergency use to treat an adverse event (AE). Patients were required to stay at the hospital facility for ≥48 hours after surgery, and they received a multimodal pain regimen until discharge (oral acetaminophen 975-1000 mg every 8 hours [maximum 3000 mg/d] and oral celecoxib 200 mg every 12 hours), including rescue analgesics as needed (oral immediate-release oxycodone ≤10 mg every 4 hours or as needed or, if unable to tolerate oral medication, IV morphine 2.5-5 mg or hydromorphone 0.5-1 mg every 4 hours or as needed). Patients received rescue medication only upon request for pain control. Other rescue medications and patient-controlled analgesia were prohibited.

The study's coprimary efficacy endpoints were area under the curve (AUC) of visual analog scale (VAS) pain intensity scores from 12 to 48 hours after surgery ($AUC_{12\text{-}48}$) and total opioid consumption (IV morphine equivalents, mg) from 0 to 48 hours after surgery. To reduce bias in pain assessments, pain intensity scores during periods of rescue medication administration were replaced by the highest observed score before rescue medication use. Secondary efficacy endpoints were total postsurgical opioid consumption through 72 hours (or discharge), the percentage of opioid-free patients through 48 and 72 hours (or discharge), and the time to first opioid rescue through 72 hours (or discharge). Safety endpoints included the incidence of treatment-emergent AEs (TEAEs) and serious AEs, including opioid-related AEs and TEAEs of special interest (cardiac events, neurologic events, and falls), through day 29 after surgery.

The safety population was composed of all patients who received study drug, and the efficacy population included all patients from the safety population who underwent the planned surgery. Efficacy analyses were based on actual treatment received. The coprimary efficacy endpoints were analyzed using analysis of variance with main effects of treatment and site. Because reduction in pain scores was being evaluated between treatment groups, one-tailed tests were used. A covariate analysis of $AUC_{12\text{-}48}$ of VAS pain intensity scores taking into account body mass index was also performed. Because the opioid data were not distributed normally (Shapiro-Wilk normality test, $P = .004$, $\alpha = 0.01$; Fig. 2), they were log-transformed prior to analysis, and LS means (the predicted means if there was a balanced distribution of the data) were reported instead of arithmetic means (parameter for normally distributed data) or medians. Log-transformed total opioid consumption through 48 hours was tested only if the between-group comparison of $AUC_{12\text{-}48}$ of VAS pain intensity scores was significant. The secondary efficacy endpoints were analyzed using a hierarchical, fixed-sequence, sequentially rejective approach. Total postsurgical opioid consumption through 72 hours was analyzed as described for the coprimary endpoints. The proportion of opioid-free patients was analyzed using the Cochran-Mantel-Haenszel test stratified by site. Time to first opioid rescue was analyzed using logistic regression and Kaplan-Meier methods; and a log-rank test was used to compare the survival curves. All treatment comparisons used a significance level of $P < .05$. Safety endpoints were summarized descriptively by treatment group.

Patient disposition is summarized in the Appendix (Fig. A1). Recruitment was stopped based on an estimate of power based on blinded data, which showed that adequate power was reached despite the lower than targeted sample size. According to this power analysis, 70 evaluable patients per treatment group were needed to achieve 80% power to detect a 40-point difference in AUC of VAS pain intensity scores (common standard deviation [SD] 67.3) and a 30% difference in log-transformed total opioids (common SD 0.67) between treatment groups at a one-sided 0.05 alpha level with sequential testing. The sample size of 70 patients per treatment group provided 96% power to detect a 40-point difference in AUC of VAS pain intensity scores, 83% power to detect a 30% difference in log-transformed total opioids, and 80% power to detect both. The safety and efficacy populations each included 139

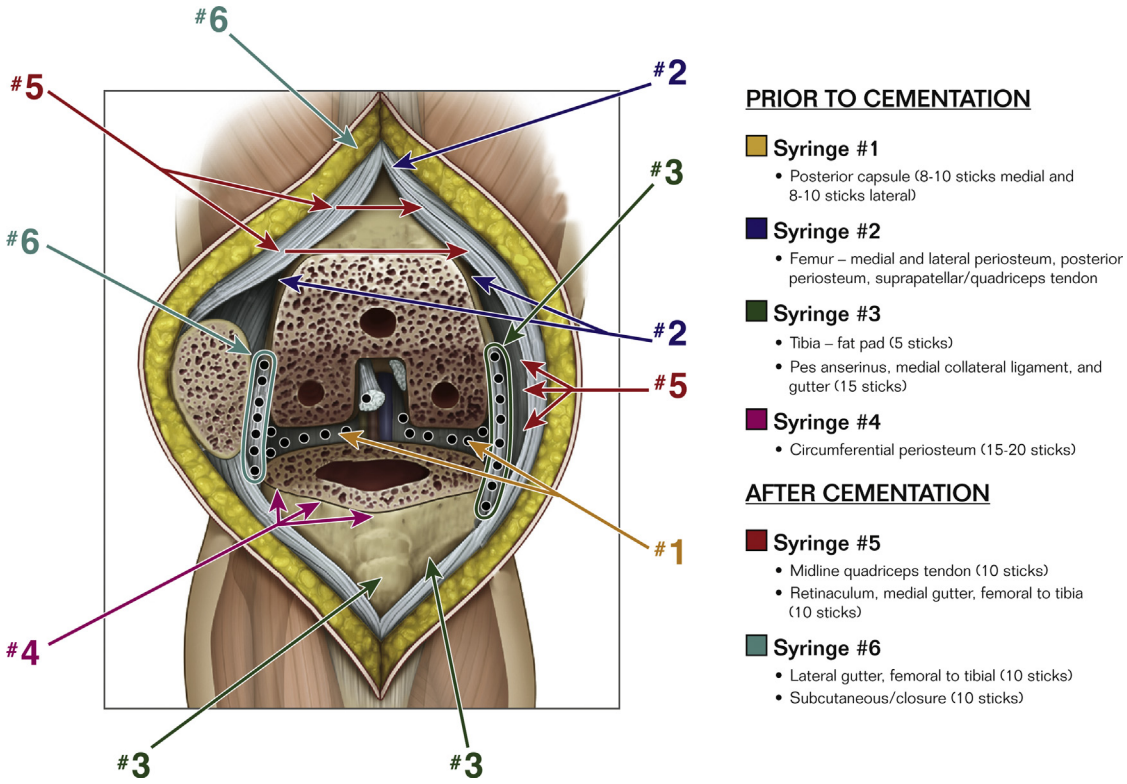

Fig. 1. Drug infiltration technique for total knee arthroplasty. Reproduced with permission from Dysart et al. [20].

patients (with LB, $n = 70$; without LB, $n = 69$). Demographic, clinical, and surgery characteristics were similar in the 2 treatment groups (Table 1). Mean age of the overall population was 66 years, 59.0% were women, and 87.8% were white. Most patients were American Society of Anesthesiologists classification 2 (61.2%) or 3 (35.3%), and the mean VAS score was 1.90 (range 0-10). Mean duration of surgery was 1.5 hours (range 0.6-3.4), with a tourniquet and drain used in 84.2% and 44.6% of the cases, respectively. The most common intraoperative medications administered were fentanyl (63.3%), followed by fentanyl citrate (1.4%). In the LIA without LB group, 1 patient received hydromorphone intraoperatively and 1 patient received morphine intraoperatively.

Results

LIA with LB significantly improved pain scores compared with LIA without LB (Fig. 3). Mean (SD) $AUC_{12\text{-}48}$ of VAS pain intensity scores, the coprimary efficacy endpoint, was 180.8 (94.80) with LB and 209.3 (78.97) without LB, with a significant least squares (LS) mean treatment difference (−26.88, $P = .0381$). A significant difference between treatment groups was also observed in a covariate analysis taking into account body mass index ($P = .017$).

LIA with LB also significantly reduced total opioid consumption (Fig. 4). LS geometric mean (standard error) total opioid consumption from 0 to 48 hours after surgery was 18.7 (7.74) mg with

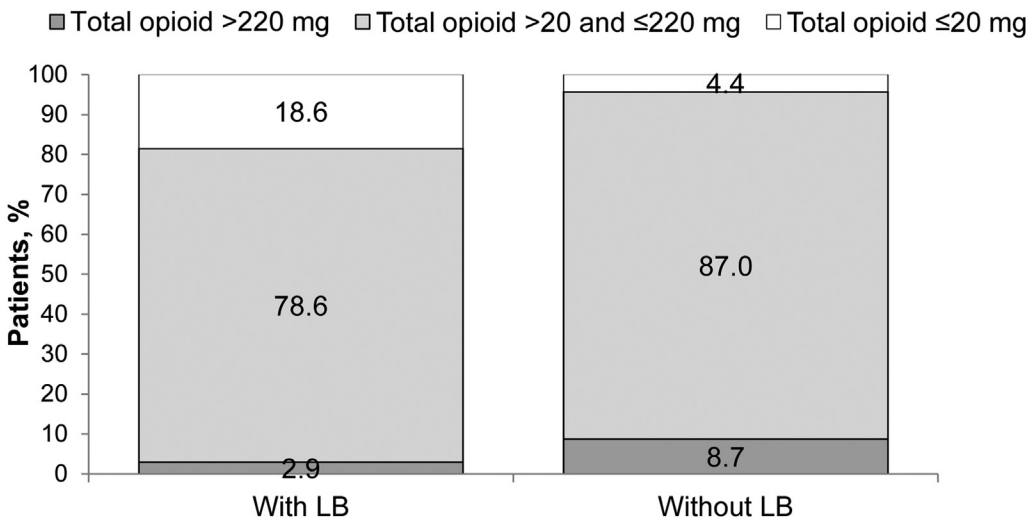

Fig. 2. Categorical distribution of total opioid consumption data. Chi-square test for 2-way table yielded a P value of .015, indicating that the proportions in each category are significantly different with vs without LB.

Table 1
Baseline Characteristics.

Characteristic[a]	With LB ($n = 70$)	Without LB ($n = 69$)	Total ($N = 139$)
Age (y)	66 (8.61)	66 (7.21)	66 (7.92)
Women, *n* (%)	43 (61.4)	39 (56.5)	82 (59.0)
Race, *n* (%)			
White	61 (87.1)	61 (88.4)	122 (87.8)
Black	7 (10.0)	5 (7.2)	12 (8.6)
Other	2 (2.9)	3 (4.3)	5 (3.6)
BMI (kg/m^2)	32.4 (5.81)	31.3 (5.19)	31.9 (5.52)
ASA classification, *n* (%)			
1	3 (4.3)	2 (2.9)	5 (3.6)
2	45 (64.3)	40 (58.0)	85 (61.2)
3	22 (31.4)	27 (39.1)	49 (35.3)
VAS score (cm)	1.91 (2.12)	1.89 (2.24)	1.90 (2.17)
Right TKA, *n* (%)	39 (55.7)	44 (63.8)	83 (59.7)
Duration of surgery (h)	1.5 (0.53)	1.5 (0.53)	1.5 (0.53)
Total incision length (cm)	$n = 65$	$n = 66$	$n = 131$
	14.0 (2.89)	14.7 (2.64)	14.3 (2.78)
Tourniquet used, *n* (%)	61 (87.1)	56 (81.2)	117 (84.2)
Duration (min)	$n = 60$	$n = 54$	$n = 114$
	63.6 (40.18)	68.2 (36.14)	65.8 (38.22)
Maximum inflation pressure (mm Hg)	$n = 61$	$n = 55$	$n = 116$
	275.8 (33.29)	274.1 (34.01)	275.0 (33.50)
Drain used, *n* (%)	34 (48.6)	28 (40.6)	62 (44.6)
Duration (h)	$n = 28$	$n = 23$	$n = 51$
	30 (13.32)	38 (23.15)	33 (18.68)

ASA, American Society of Anesthesiologists; BMI, body mass index.
[a] Mean (SD) unless otherwise specified.

LB and 84.9 (35.50) mg without LB, with a significant LS ratio (0.220 [95% confidence interval 0.070-0.692], $P = .0048$). Total inpatient postsurgical opioid consumption from 0 to 72 hours also showed a significant reduction with (20.9 [8.70]) vs without (93.6 [39.43]) LB (Fig. 4; LS ratio 0.223 [95% confidence interval 0.070-0.707], $P = .0108$).

Consistent with these effects on pain and total postsurgical opioid consumption, LIA with LB significantly increased the proportion of opioid-free patients and significantly delayed time to first opioid rescue compared with LIA without LB. Overall, 90% of patients receiving LIA with LB took opioid rescue medication vs 100% of patients receiving LIA without LB. The percentage of opioid-free patients through 48 and 72 hours (or discharge) was significantly greater (all $P < .01$) with vs without LB (Fig. 5). The time to

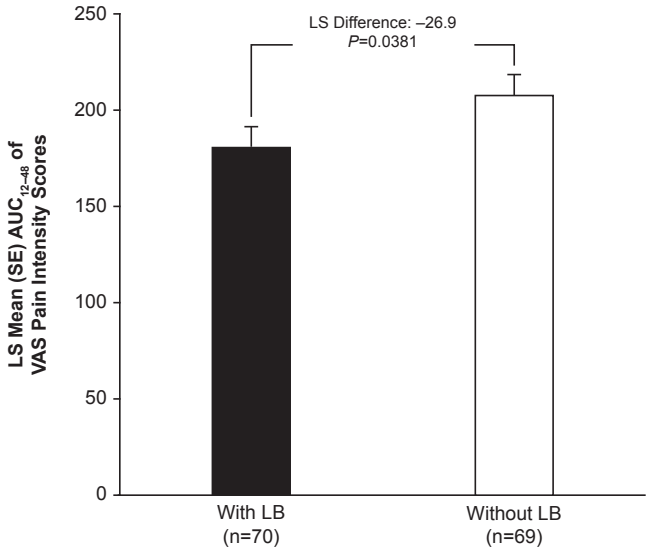

Fig. 3. LS mean (SE) $AUC_{12\text{-}48}$ of VAS pain intensity scores. SE, standard error.

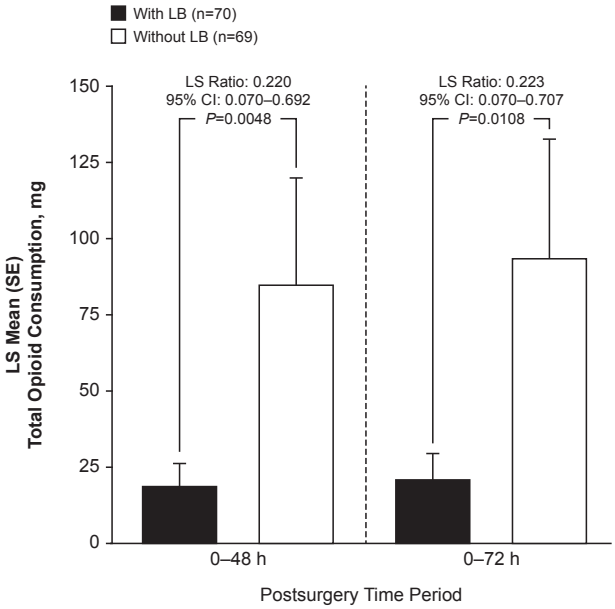

Fig. 4. LS geometric mean (SE) total opioid consumption by postsurgery time period. CI, confidence interval; SE, standard error.

first opioid rescue ranged from 0.25 to 48 hours (censored) with LB and from 0.27 to 33 hours without LB, and the time to rescue of 50% of patients was 4.1 and 2.9 hours, respectively, with a significant difference between the survival curves ($P = .0230$; Fig. 6).

Both treatments were well tolerated (Table 2). The incidence of ≥1 TEAE was 64.3% with LB and 56.5% without LB, and most TEAEs were mild or moderate in severity. The most common TEAEs were nausea, dizziness, and muscle spasms. Opioid-related AEs and AEs of interest are summarized in Table 2. One patient in each group experienced a serious AE (incision-site cellulitis in LIA with LB group, influenza in LIA without LB group); both events resolved and were considered unrelated or unlikely to be related to study drug. No patient discontinued the study because of a TEAE.

Discussion

The PILLAR study was designed to address the limitations of previous studies of LIA with LB in TKA that may have contributed to discrepant results reported in the literature. The study objectives were to compare pain scores, opioid consumption, time to first opioid rescue, and safety with LIA with and without LB using a standardized infiltration protocol alongside a multimodal analgesia protocol. The study results show that LIA with LB produced statistically significant and clinically meaningful improvements for all efficacy endpoints with no unexpected safety concerns.

With 140 patients, the PILLAR study was moderate in size. Although this can be considered a study limitation, it is a reflection of the stringent inclusion and exclusion criteria that were applied (eg, exclusion for previous use of short- or long-acting opioids or history of contralateral TKA), which helped to minimize potential confounding elements. Within the opioid-sparing multimodal analgesia protocol, opioids were the only permitted rescue medication. Because of this, opioid consumption was minimal, but the results may in fact underestimate the potential for further reduction in opioid consumption in clinical practice, wherein nonopioid analgesics may be used as the first line of rescue. Recovery time and healthcare costs were not evaluated in the PILLAR study, and lengths of stay could not be assessed

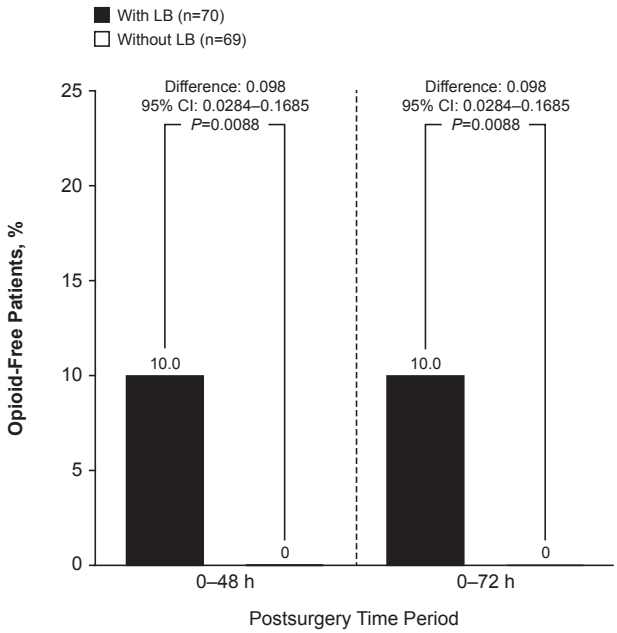

Fig. 5. Percentage of opioid-free patients by postsurgery time period. CI, confidence interval.

because all patients were required to remain in the hospital for 2 days. However, this requirement ensured that opioid consumption and pain data, which could be assessed as AUC instead of discrete time points, remained reliable and valid throughout the study period. Thus, although introducing certain limitations, the strict study protocol helped to ensure consistent and meaningful analgesic outcomes.

A key strength of the PILLAR study was the use of a meticulous and standardized infiltration protocol. The infiltration techniques reflect the extensive clinical experience of various practitioners, including members of the investigative team, with perioperative local anesthetics, including LB, as part of multimodal pain management in TKA. Important elements include expanding the drug to an adequate total volume, use of numerous, small-volume injections throughout the layers of incision, use of the right needle size to minimize leakage, and admixing with bupivacaine HCl to provide adequate early analgesia. A similar approach has been used successfully by Connelly et al [22] and is described in a recent consensus recommendation [23]. Rigorous field training was instituted to ensure consistent use of these techniques across study sites. A straightforward opioid-sparing multimodal pain

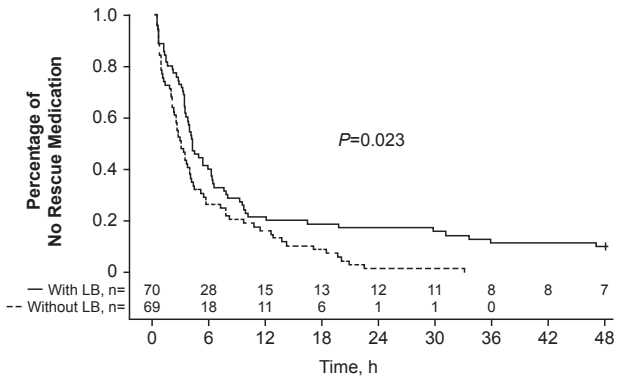

Fig. 6. Kaplan-Meier plot of time to first rescue medication through 48 hours postsurgery.

Table 2
Summary of Treatment-Emergent Adverse Events (Safety Population).

AE, *n* (%)	With LB ($n = 70$)	Without LB ($n = 69$)	Total ($N = 139$)
≥1 TEAE	45 (64.3)	39 (56.5)	84 (60.4)
≥1 related TEAE	4 (5.7)	2 (2.9)	6 (4.3)
Discontinuation due to a TEAE	0	0	0
≥1 SAE	1 (1.4)	1 (1.4)	2 (1.4)
Most common TEAEs (≥5% in either group)			
Nausea	21 (30.0)	22 (31.9)	43 (30.9)
Dizziness	3 (4.3)	8 (11.6)	11 (7.9)
Muscle spasms	6 (8.6)	0	6 (4.3)
Vomiting	5 (7.1)	5 (7.2)	10 (7.2)
Hypokalemia	4 (5.7)	1 (1.4)	5 (3.6)
ORAEs,[a]			
Constipation	3 (4.3)	3 (4.3)	6 (4.3)
Pruritus	3 (4.3)	0	3 (2.2)
Sedation	0	0	0
TEAEs of special interest,[b]			
Mental status changes	0	2 (2.9)	2 (1.4)
Bradycardia	1 (1.4)	1 (1.4)	2 (1.4)
Arrhythmia	0	1 (1.4)	1 (0.7)
Falls	0	1 (1.4)	1 (0.7)

ORAEs, opioid-related adverse events; SAE, serious adverse event.
[a] Nausea and vomiting are reported under the most common TEAEs.
[b] Dizziness is reported under the most common TEAEs.

management protocol including scheduled acetaminophen/celecoxib and opioids only as needed for rescue was utilized. This protocol allowed for pain to be appropriately and safely managed with minimal and, in some cases, no opioids.

As mentioned previously, some studies of LIA with LB in TKA have reported positive results [9–11], whereas others have reported neutral or negative results [12–19]. These disparities may be partly attributable to differences in study design and methodology, including infiltration techniques. For example, the neutral results reported by Schroer et al [19] could reflect several methodologic factors, including nonequivalence of the bupivacaine HCl dose in the LB (75 mg) and control groups (150 mg), which may have led to greater initial pain in the LB vs control group, and an inability to "catch up" pain control at later periods (data were not stratified by time periods). Other limitations included use of a suboptimal infiltration volume (LB 50 mL, bupivacaine HCl 60 mL), assessment of pain scores at discrete time points, and lack of opioid minimization [19]. Similar limitations related to infiltration techniques (including partial infiltration, overly large gauge needle, no bupivacaine HCl bridging) [13–17], pain assessment or primary outcome [12–16,18], and opioid minimization [15,16] are evident in other previous studies reporting negative or neutral findings. In the PILLAR study, the treatment groups received equal amounts of bupivacaine HCl; an optimal infiltration volume (120 mL) was used; pain scores were analyzed as AUC based on repeated assessments at standardized intervals; and steps such as prohibiting patient-controlled analgesia and avoiding scheduled opioids were taken to minimize opioids. Possible additional reasons for negative or neutral findings in the literature include potential lack of study power [12,13,15,18] and issues with patient selection [14,17,18]. It is worth pointing out that the primary endpoint for the PILLAR study, $AUC_{12\text{-}48}$ of VAS pain intensity scores, was chosen because a between-group difference in earlier postsurgical pain control (eg, 0-12 hours) was not expected given that both treatment groups received bupivacaine HCl.

Consistent with the current findings, a prospective, randomized, double-blind controlled trial demonstrated significant improvements in postsurgical pain scores and opioid consumption with LIA with LB vs a concentrated multidrug cocktail [10]. Patients receiving LIA with LB also reported significantly higher satisfaction with pain control overall and while in the hospital. Although this

study also had limitations (eg, potential lack of study power, lack of bupivacaine bridging, suboptimal pain assessment), this is the only randomized, double-blind controlled trial to date that used what might be considered optimal LB volume and infiltration techniques.

The reduction in opioid consumption with LIA with LB in the PILLAR study is important in light of the negative impact of opioid-related AEs on patient outcomes [24] and the opioid epidemic. Orthopedic surgery has one of the highest rates of opioid prescribing [25], which puts patients at increased risk for chronic opioid use, misuse, and abuse [26–28]. The impact of the current opioid epidemic cannot be overstated, with 91 Americans dying from opioid overdose each day [29]. The American Academy of Orthopaedic Surgeons has recently called for orthopedic surgeons to implement patient education and pain management strategies to reduce opioid use [30]. In addition, the American Academy of Orthopaedic Surgeons has launched a multimedia campaign to further raise awareness of this issue among patients and doctors [31]. Orthopedic surgeons may play a substantial role in addressing these concerns by reducing the number of patients who remain on chronic opioid treatment for months and years after the acute postsurgical period. For patients suspected to be at risk for opioid misuse, such as individuals with a personal or family history of substance abuse, history of depression or bipolar disorder, or aberrant behavior (eg, early refill requests) [25], opioid-free surgery should be considered a realistic goal moving forward.

The potential for LB to facilitate opioid-free surgery and ambulatory joint arthroplasty programs [32] is relevant to another key topic, healthcare costs. Although the current data demonstrate improved outcomes using LIA with LB, evidence of reasonable costs is needed to further establish the benefit of this approach. Overall, cost-benefit is driven by not only the price of the medication but also factors such as operative time, use of opioids and pain pumps and their associated complications, pace of functional recovery, hospital lengths of stay, and readmissions. Although the cost of LB is $300 higher than that of bupivacaine HCl, retrospective study data suggest a net reduction in hospital costs compared with standard of care [33–35]. A case-control study of >2000 joint arthroplasties performed using a standard of care multimodal pain protocol with periarticular injection or a protocol including LB periarticular injection demonstrated a significant improvement in pain outcomes and an average reduction in hospital overall direct cost of $1246 per patient using LB [36]. A forthcoming manuscript will further address costs by reporting related endpoints such as discharge readiness, lengths of stay, incidences of readmission, and health services use after discharge in the PILLAR study.

In addition to cost data, comparisons with multidrug cocktails would further inform the clinical effectiveness of LB. Refinement of patient demographics, genetics, and cytokine levels to more accurately predict responders and nonresponders is worthy of future study. Studies targeting specific patient populations, such as opioid-naive patients, patients who abuse opioids, and patients undergoing other types of joint arthroplasty, could also be fruitful as the field continues to evolve.

Conclusions

The PILLAR study provides data on the efficacy and safety of LB when administered using optimal infiltration techniques as part of a standardized opioid-sparing multimodal pain management protocol. Results show that an opioid-sparing multimodal pain management approach using LIA with LB can safely manage pain while further reducing or eliminating the need for opioids following TKA.

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Appendix A. Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.arth.2017.07.024.

References

[1] Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. J Surg Orthop Adv 2014;23:22–36.
[2] Elmallah RK, Cherian JJ, Pierce TP, Jauregui JJ, Harwin SF, Mont MA. New and common perioperative pain management techniques in total knee arthroplasty. J Knee Surg 2016;29:169–78.
[3] Hamilton DF, Lane JV, Gaston P, Patton JT, Macdonald D, Simpson AH, et al. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. BMJ Open 2013;3:e002525.
[4] American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248–73.
[5] Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, 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;17:131–57.
[6] Hu B, Lin T, Yan SG, Tong SL, Yu JH, Xu JJ, et al. Local infiltration analgesia versus regional blockade for postoperative analgesia in total knee arthroplasty: a meta-analysis of randomized controlled trials. Pain Physician 2016;19:205–14.
[7] Fan L, Zhu C, Zan P, Yu X, Liu J, Sun Q, et al. The comparison of local infiltration analgesia with peripheral nerve block following total knee arthroplasty (TKA): a systematic review with meta-analysis. J Arthroplasty 2015;30:1664–71.
[8] EXPAREL® (bupivacaine liposome injectable suspension). Full prescribing information. Parsippany, New Jersey: Pacira Pharmaceuticals, Inc; 2016.
[9] Barrington JW, Emerson RH, Lovald ST, Lombardi AV, Berend KR. No difference in early analgesia between liposomal bupivacaine injection and intrathecal morphine after TKA. Clin Orthop Relat Res 2017;475:94–105.
[10] Snyder MA, Scheuerman CM, Gregg JL, Ruhnke CJ, Eten K. Improving total knee arthroplasty perioperative pain management using a periarticular injection with bupivacaine liposomal suspension. Arthroplast Today 2016;2:37–42.
[11] Heim EA, Grier AJ, Butler RJ, Bushmiaer M, Queen RM, Barnes CL. Use of liposomal bupivacaine instead of an epidural can improve outcomes following total knee arthroplasty. J Surg Orthop Adv 2015;24:230–4.
[12] Amundson AW, Johnson RL, Abdel MP, Mantilla CB, Panchamia JK, Taunton MJ, et al. A three-arm randomized clinical trial comparing continuous femoral plus single-injection sciatic peripheral nerve blocks versus periarticular injection with ropivacaine or liposomal bupivacaine for patients undergoing total knee arthroplasty. Anesthesiology 2017;126:1139–50.
[13] Alijanipour P, Tan TL, Matthews CN, Viola JR, Purtill JJ, Rothman RH, et al. Periarticular injection of liposomal bupivacaine offers no benefit over standard bupivacaine in total knee arthroplasty: a prospective, randomized, controlled trial. J Arthroplasty 2017;32:628–34.
[14] Meneghini RM, Bagsby D, Ireland PH, Ziemba-Davis M, Lovro LR. Liposomal bupivacaine injection technique in total knee arthroplasty. J Knee Surg 2017;30:88–96.
[15] Collis PN, Hunter AM, Vaughn MD, Carreon LY, Huang J, Malkani AL. Periarticular injection after total knee arthroplasty using liposomal bupivacaine vs a modified Ranawat suspension: a prospective, randomized study. J Arthroplasty 2016;31:633–6.
[16] Jain RK, Porat MD, Klingenstein GG, Reid JJ, Post RE, Schoifet SD. The AAHKS clinical research award: liposomal bupivacaine and periarticular injection are not superior to single-shot intra-articular injection for pain control in total knee arthroplasty. J Arthroplasty 2016;31:22–5.
[17] Klug MJ, Rivey MP, Carter JT. Comparison of intraoperative periarticular injections versus liposomal bupivacaine as part of a multimodal approach to pain management in total knee arthroplasty. Hosp Pharm 2016;51:305–11.
[18] Schwarzkopf R, Drexler M, Ma MW, Schultz VM, Le KT, Rutenberg TF, 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;31:1702–5.
[19] Schroer WC, Diesfeld PG, LeMarr AR, Morton DJ, Reedy ME. Does extended-release liposomal bupivacaine better control pain than bupivacaine after total knee arthroplasty (TKA)? A prospective, randomized clinical trial. J Arthroplasty 2015;30:64–7.
[20] Dysart S, Snyder MA, Mont MA. A randomized, multicenter, double-blind study of local infiltration analgesia with liposomal bupivacaine for post-surgical pain following total knee arthroplasty: rationale and design of the PILLAR trial. Surg Technol Int 2016;30:261–7.
[21] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: guideline for good clinical practice E6 (R1). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf; 1996 [accessed 28.06.17].
[22] Connelly JO, Edwards PK, Mears SC, Barnes CL. Technique for periarticular local infiltrative anesthesia delivery using liposomal bupivacaine in total knee arthroplasty. J Surg Orthop Adv 2015;24:263–6.
[23] Joshi GP, Cushner FD, Barrington JW, Lombardi Jr AV, Long WJ, Springer BD, et al. Techniques for periarticular infiltration with liposomal bupivacaine for the management of pain after hip and knee arthroplasty: a consensus recommendation. J Surg Orthop Adv 2015;24:27–35.
[24] Kessler ER, Shah M, Gruschkus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. Pharmacotherapy 2013;33:383–91.
[25] Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. J Am Acad Orthop Surg 2015;23:267–71.
[26] Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid prescribing at hospital discharge contributes to chronic opioid use. J Gen Intern Med 2016;31:478–85.
[27] Kelly MA. Current postoperative pain management protocols contribute to the opioid epidemic in the United States. Am J Orthop 2015;44:S5–8.
[28] Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Slavin K, Trescot AM, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician 2017;20:S3–s92.
[29] Centers for Disease Control and Prevention. Understanding the epidemic. Drug overdose deaths in the United States continue to increase in 2015. https://www.cdc.gov/drugoverdose/epidemic/ [accessed 07.04.17].
[30] American Academy of Orthopaedic Surgeons. Information statement. Opioid use, misuse, and abuse in orthopaedic practice. http://www.aaos.org/uploadedFiles/PreProduction/About/Opinion_Statements/advistmt/1045%20Opioid%20Use,%20Misuse,%20and%20Abuse%20in%20Practice.pdf; 2015 [accessed 07.04.17].
[31] American Academy of Orthopaedic Surgeons. New AAOS public service campaigns tackle opioid misuse, childhood obesity. http://newsroom.aaos.org/media-resources/news/opioid-abuse-childhood-obesity.tekprint; 2017 [accessed 07.02.17].
[32] Barrington JW, Halaszynski TM, Sinatra RS, Expert Working Group on Anesthesia and Orthopaedics Critical Issues in Hip and Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. Am J Orthop 2014;43:S1–16.
[33] Asche CV, Ren J, Kim M, Gordon K, McWhirter M, Kirkness CS, et al. Local infiltration for postsurgical analgesia following total hip arthroplasty: a comparison of liposomal bupivacaine to traditional bupivacaine. Curr Med Res Opin 2017;33:1283–90.
[34] Kirkness CS, Asche CV, Ren J, Kim M, Rainville EC. Cost-benefit evaluation of liposomal bupivacaine in the management of patients undergoing total knee arthroplasty. Am J Health Syst Pharm 2016;73:e247–54.
[35] Cien AJ, Penny PC, Horn BJ, Popovich JM, Taunt CJ. Comparison between liposomal bupivacaine and femoral nerve block in patients undergoing primary total knee arthroplasty. J Surg Orthop Adv 2015;24:225–9.
[36] Barrington JW, Olugbode O, Lovald S, Ong K, Watson H, Emerson Jr RH. Liposomal bupivacaine: a comparative study of more than 1000 total joint arthroplasty cases. Orthop Clin North Am 2015;46:469–77.