J Shoulder Elbow Surg (2021) 30, 587–598

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

Liposomal bupivacaine interscalene nerve block in shoulder arthroplasty is not superior to plain bupivacaine: a double-blinded prospective randomized control trial

Steven J. Hattrup, MD[a,*], Andrew S. Chung, DO[a], David M. Rosenfeld, MD[b], Lopa Misra, DO[b], Veerandra Koyyalamudi, MBBS[b], Matthew L. Ritz, MD[b], John M. Tokish, MD[a]

[a]*Department of Orthopedic Surgery, Mayo Clinic Arizona, Phoenix, AZ, USA*
[b]*Department of Anesthesiology, Mayo Clinic Arizona, Phoenix, AZ, USA*

Background: Interscalene brachial plexus blocks are a common modality used to provide adjunctive pain relief with shoulder replacement surgery. In 2018, the Federal Drug Administration approved the use of liposomal bupivacaine (LB) for such nerve blocks. We sought to evaluate whether this formulation of bupivacaine would provide superior pain relief for shoulder replacement patients over standard bupivacaine alone. Our hypotheses were that in the LB cohort the average postoperative pain score over the first 72 hours would be significantly lower, time to block cessation would be longer, total opioid consumption would be lower, and the average patient satisfaction score regarding their pain management would be higher.

Materials and methods: A randomized, double-blinded study was designed comparing primary shoulder replacement surgery after an interscalene block with 25 mL of 0.5% plain bupivacaine vs. 133 mg of LB with 7.5 mL of 0.5% and 7.5 mL of 0.25% plain bupivacaine. A total of 104 patients were included in the study, with an equal number in each study arm. Patients' visual analog pain scores (VAPS) were followed for their inpatient stay, first 3 full outpatient days, and at a 3-week follow-up. Use of opioid medication was recorded for the same intervals and converted to morphine milligram equivalents. The time to first opioid rescue was documented, as well as the patients' satisfaction with their pain management at both the 3-day and 3-week intervals.

Results: No clinically relevant advantage to the use of LB over plain bupivacaine was found. During the second postoperative day, the mean VAPS was 2.4 with LB vs. 3.3 in the standard cohort ($P = .0409$). The only other statistically significant finding was a higher VAPS with LB during the third full day home compared with standard bupivacaine (4.0 vs. 2.8, respectively, $P = .0197$). Both of these differences were less than the minimal clinically important difference of 2 for the VAPS. Analysis of the VAPS for the first and third postoperative days, the first and second full days home, and at 3 weeks revealed no significant difference. Similarly, there was no significant difference in time to first opioid rescue, total morphine milligram equivalent use, and patient satisfaction with pain management.

Conclusion: When used for an interscalene block to provide adjunctive pain relief in shoulder replacement surgery, the addition of LB to plain bupivacaine provides no additional clinically important benefit to the patient's pain experience over standard bupivacaine.

Institutional review board approval was received from Mayo Clinic (no. 18-005366).

*Reprint requests: Steven J. Hattrup, MD, Department of Orthopedic Surgery, Mayo Clinic Arizona, 5777 East Mayo Blvd, Phoenix, AZ 85054, USA.

E-mail address: hattrup.steven@mayo.edu (S.J. Hattrup).

https://doi.org/10.1016/j.jse.2020.09.017

Level of evidence: Level I; Randomized Controlled Trial; Treatment Study

Keywords: Shoulder; arthroplasty; interscalene block; liposomal bupivacaine; pain management; visual analogue pain score

Pain management after surgery is a subject of much interest for patients and their care team. Elevated pain levels or the prospect of severe pain is frightening for the patient and may have secondary adverse effects. Patient satisfaction, sense of well-being, and even surgical outcomes can be affected by pain.[11,20] Physiologic consequences of pain can include tachycardia, tachypnea, hypoventilation, impaired sleep, and development of chronic pain.[11,17] Inadequate pain management has been shown to not only increase hospital length of stay, but increase the risk of thromboembolic events, pulmonary complications, and chronic pain syndromes.[5,32,33]

The goals of proper pain management include not only the desire to lessen the unpleasant aspects of surgery, but also to aid in the rapid mobilization of patients. Patients are able to have their surgery as outpatients, or with shorter hospital stays, lessening the burden on the health care system and enabling the patients to recuperate in their home environment.[8-10,24]

Historically, moderate-to-severe pain has been treated with opioid medications. These medications come with their own consequences though. Kessler et al,[23] in a review of over 37,000 postoperative patients, found that the vast majority received opioids postoperatively, and 13.6% of these patients experienced an opioid-related adverse drug event. These events were associated with longer hospital stays, higher cost of care, increased readmission rates, and higher mortality rates.[23] The use of opioid medications for postoperative pain has well-recognized side effects. These include sedation, dizziness, nausea and vomiting, constipation, respiratory depression, and the potential of long-term dependence.[4,6,12,19,34] Opioid postsurgical medications have also been implicated in the drug addiction crisis in the United States.[3,19]

Consequently, there has been increasing interest in the development of multimodal pain control regimens. Rather than limiting the management of pain to opioids, these protocols seek to reduce opioid utilization with a combination of medications such as acetaminophen, nonsteroidal anti-inflammatories, N-methyl-D-aspartate (NMDA) antagonists, gabapentin, and local anesthetics.[17,27]

Regional analgesia through the use of local anesthetic agents is a commonly employed strategy for pain management. In shoulder surgery, specifically, an interscalene or supraclavicular brachial plexus nerve block in conjunction with general anesthesia has been used for shoulder replacement surgery. In a review of over 17,000 patients receiving shoulder replacement between 1997 and 2011, Stundner et al[30] found that 21% had received an upper extremity nerve block, with no detectable increase in complications. Effective analgesia with less need for opioid medication and shorter hospital stay has been demonstrated with the adjunctive use of brachial plexus blocks.[21,29] These nerve blocks have typically been performed with long acting local anesthetics such as ropivacaine or bupivacaine, both of which provide an analgesia benefit of 8-12 hours.[1,17]

In 2011, liposomal bupivacaine (LB) (Exparel; Pacira Pharmaceuticals, San Diego, CA, USA) was approved by the US Food and Drug Administration (FDA) for use as a local anesthetic for surgical site infiltration. LB is composed of a phospholipid bilayer that encapsulates bupivacaine, extending drug delivery for up to 72 hours and potentially extending periods of regional analgesia. Early studies evaluating LB wound infiltration noted lower subjective pain scores, increased time to first opiate medication, and decreased total opiate requirements when compared with placebo.[16,18] However, a recent systematic review of all randomized controlled trials in orthopedic surgery across a variety of procedures does not support the routine use of local infiltrative LB over other local or regional anesthetic modalities.[2]

In April, 2018, LB was FDA-approved for use in interscalene nerve blocks in the setting of shoulder surgery. There is limited data comparing LB with traditional agents in this population. The objective of this study is to determine if LB in combination with standard bupivacaine would prolong the duration of an interscalene block, improve pain scores, decrease opioid utilization, and improve patient satisfaction in the postoperative period when compared with standard bupivacaine alone. Our primary hypothesis was that the average postoperative pain score over the first 72 hours would be significantly lower in the LB group. Our secondary hypotheses were: (1) time to block cessation would be longer in the LB group than the standard bupivacaine group; (2) total opioid consumption would be lower in the LB group; (3) the average patient satisfaction score regarding their pain management would be higher in the LB group.

Methods

A prospective, double-blinded randomized controlled trial was undertaken at a single institution between November 2018 and January 2020, to study the potential differences between an interscalene block for shoulder replacement with plain bupivacaine with and without LB. All adults patients (>18 years of age)

undergoing standard or reverse total shoulder arthroplasty for the primary diagnoses of glenohumeral arthritis or cuff tear arthropathy were considered eligible for the study. All surgeries were performed by 2 experienced shoulder surgeons. Nonelective procedures including infection, tumor, or trauma cases, and all revision surgeries were excluded. A list of all inclusion and exclusion criteria is provided in Table I. Study approval was obtained from the relevant institutional review board. Study funding was provided by an internal institutional grant. This study was registered at ClinicalTrials.gov (study no. NCT03663283).

Patient randomization and study blinding

Patients were randomized to receive either an interscalene brachial plexus block with the intervention drug (133 mg [10 mL] of LB mixed with 7.5 mL of 0.5% and 7.5 mL of 0.25% plain bupivacaine) or control (25 mL of 0.5% plain bupivacaine).[15] Doses were determined using 0.5% bupivacaine in 25 mL as a typical standard of care control and investigational doses in the same volume comfortably adhering to the labeled maximum 133 mg of LB in a 2:1 ratio with plain bupivacaine. A randomized block strategy with varying block sizes was used.[14] The research pharmacist randomized and prepared all block medications. The medication syringe was enclosed in an opaque covering (black tape) to obscure visual clues to the nature of the administered medication. Patients, care team, study team members collecting and recording data, and statisticians were blinded to the randomization assignment. For safety reasons, all patients in both treatment arms of the study wore an identifying wrist band that stated that they had received LB to avoid further administration of any local anesthetic. This was to avoid potential harm for the patients who had already received LB, yet preserve the blinded nature of the study.

Anesthesia and analgesia

All peripheral nerve blocks were performed with ultrasound guidance by an attending anesthesiologist experienced in the technique or an experienced anesthesiology resident with direct attending supervision and assistance. Preoperative sedation was limited to 4 mg of intravenous midazolam. Eight milligrams of dexamethasone was given intravenously at the time of the nerve block. Block success was assessed preoperatively based on the presence of shoulder abductor weakness and re-assessed on arrival to the postanesthesia care unit (PACU).

All patients underwent general endotracheal anesthesia using propofol, fentanyl, rocuronium or succinylcholine, sevoflurane in air-oxygen, and ondansetron. Fentanyl was limited to a maximum of 250 μg intraoperatively. Opioids administered in the PACU, if any, were considered as part of inpatient pain medication and were included in hospital morphine milligram equivalents (MMEs). Reversal of muscle relaxant was with either neostigmine and glycopyrrolate or sugammadex.

Patients were discharged from the PACU to the surgical floor on a standardized pain regimen that included a combination of the following medications: scheduled acetaminophen 1000 mg every 8 hours, first-line therapy tramadol 50 mg every 6 hours as needed for visual analog pain score (VAPS) $\leq$3, tramadol 100 mg every 6 hours as needed for VAPS 4-6; second-line therapy oxycodone 5 mg every 4 hours as needed for VAPS 4-6; oxycodone 10 mg every 4 hours as needed for VAPS 7-10; and for severe break through pain intravenous fentanyl 25 mcg every 2 hours as needed.

At hospital discharge, a prescription for one of the following pain medications was provided: oxycodone 5 or 10 mg every 4 hours as needed, oxycodone-acetaminophen 5/325 mg or 10/325 mg every 4 hours as needed, hydrocodone-acetaminophen 5/325

Table I Inclusion and exclusion criteria

Inclusion	Exclusion
18 yr of age	Nonelective cases:
All primary standard or reverse total shoulder arthroplasties	Infection, tumor, trauma, revision surgery
Ability to give informed consent as outlined by the institutional review board	Weight <50 kg
Ability to participate in the postoperative electronic survey and/or able to maintain a written diary of events	Patient with contraindications to regional anesthesia including allergy or hypersensitivity to amide-type local anesthetics
	Patient allergy to any component of medication regimen, for example, amide-type local anesthetics, oxycodone, hydromorphone, fentanyl
	Chronic pain patients with a history of chronic opioid use (defined as 20 mg of morphine milligram equivalent/d for more than 30 d preoperatively)
	Concurrent painful physical condition that requires analgesic treatment that is not related to the shoulder surgery (chronic peripheral neuropathy, radiculopathy, or other neurologic disorder)
	Severe hepatic disease defined by elevated liver function tests above normal
	Respiratory disease that contraindicates an interscalene nerve block (elevated contralateral hemidiaphragm, contralateral pneumonectomy, or severe COPD with FEV1 < 50% predicted, and 02 dependence)
	Pregnancy

COPD, chronic obstructive pulmonary disease; *FEV1*, forced expiratory volume in 1 second.

Table II Study participant demographics are detailed

Variable	Total (N = 104)	Plain bupivacaine (N = 52)	Liposomal bupivacaine (N = 52)	*P* value
Patient age				
Mean (SD)	69.6 (8.62)	69.2 (10.15)	70.0 (6.84)	.5027*
Median	69.5	68.5	70	
Gender, n (%)				
Male	58 (55.8)	28 (53.8)	30 (57.7)	.8436†
Female	46 (44.2)	24 (46.2)	22 (42.3)	
BMI				
Mean	29.3 (4.75)	29.2 (5.46)	29.4 (3.98)	.5651*
Median	29.2	28.9	29.6	
Side of surgery, n (%)				
Left	47 (45.2)	24 (46.2)	23 (44.2)	1.000†
Right	57 (54.8)	28 (53.8)	29 (55.8)	
Type of replacement, n (%)				
Anatomic	56 (53.8)	33 (63.5)	23 (44.2)	.0762†
Reverse	48 (46.2)	19 (36.5)	29 (55.8)	
Operative time (min)				
Mean (SD)	73.9 (14.65)	72.7 (11.86)	75.2 (17.02)	.6630*
Median	72.5	72	72.5	
Prior shoulder surgery, n (%)				
No	64 (61.5)	33 (63.5)	31 (59.6)	.8404†
Yes	40 (38.5)	19 (36.5)	21 (40.4)	
ASA classification, n (%)				
ASA I	3 (2.9)	1 (1.9)	2 (3.8)	.6183†
ASA II	75 (72.1)	36 (69.2)	39 (75.0)	
ASA III	26 (25.0)	15 (28.8)	11 (21.2)	
Charleston Comorbidity Index				
Mean (SD)	1.2 (1.67)	1.3 (1.82)	1.2 (1.51)	.8949*
Median	1	1	0	

SD, standard deviation; *BMI*, body mass index; *ASA*, American Society of Anesthesiologists.
* Wilcoxon rank sum *P* value.
† Fisher exact *P* value.

Table III Preoperative patient recorded outcomes

Variable	Total (N = 104)	Plain bupivacaine (N = 52)	Liposomal bupivacaine (N = 52)	*P* value
VR-12				
Mean (SD)	85.2 (9.74)	84.2 (10.33)	86.1(9.11)	.4887*
Median	86.2	85.8	86.8	
SANE				
Mean (SD)	45.1 (19.73)	41.3 (16.72)	48.9 (21.85)	.1313*
Median	50	40	50	
ASES				
Mean (SD)	46.0 (14.88)	46.8 (14.96)	45.1 (14.91)	.4582*
Median	46.7	49.2	45	
SST				
Mean (SD)	4.3 (2.25)	4.2 (2.50)	4.4 (1.98)	.7604*
Median	4	4.5	4	

VR-12, Veterans RAND 12 Item Health Survey; *SD*, standard deviation; *SANE*, Single Assessment Numeric Evaluation; *ASES*, American Shoulder and Elbow Surgeons; *SST*, Simple Shoulder Test.
* Wilcoxon rank sum *P* value.

mg or 10/325 mg every 4 hours as needed for pain, or tramadol 50 or 100 mg every 6 hours as needed. The choice of the dismissal medication was left to the discretion of the operative surgeon, based on such factors as the postoperative analgesic requirements, and the patients' age, size, and comorbidities. Patients were free to use nonopioid medications as appropriate, for example, acetaminophen, ibuprofen.

Data collection

All baseline patient demographic information and medical history were recorded after consent for study participation was initially obtained (Table II). In addition to patient VAPS, the following patient-reported outcome measures were collected at the first preoperative visit: the Single Assessment Numeric Evaluation score, the Simple Shoulder Test, the American Shoulder and Elbow Surgeons score, and the Veterans RAND 12 Item Health Survey (Table III).

Patient VAPS scales were recorded every 15 minutes in the PACU immediately after surgery for the first 4 hours, then at a minimum at 4-hour intervals thereafter during the duration of their hospital stay. Both patients and nursing staff were educated on how to accurately report the time of the patient-reported cessation of the nerve blockade as the first reported postoperative pain score of 3 or greater at the surgical site. This VAPS level was chosen to be consistent with the standard hospital postoperative analgesia orders. In addition to total inpatient opioid utilization, the time until first opioid rescue after surgery was recorded.

Operative time, laterality of surgery, length of stay, and disposition at discharge from the hospital were additionally noted.

For the first 72 hours after hospital discharge, pain scores were measured using electronically managed surveys that were automatically e-mailed to each patient on a twice daily basis (on waking in the AM and just before bedtime). Finally, patient satisfaction scores (Likert scores) were e-mailed to the subjects at the end of 72 hours.

Total opioid consumption during this time frame was similarly measured based off of electronically managed surveys or a written diary on a daily basis.

During the first follow-up visit at 3 weeks, the total outpatient opioid consumption during patients' postoperative course was measured. Total opioid consumption was quantified by the number of narcotic prescription pills remaining in the patients' original plus any subsequent prescriptions. If additional narcotic prescriptions were prescribed in the postoperative period, these were also accounted for.

All opioid consumption was standardized to MMEs.[13] Finally, all complications after surgery were recorded. These included cardiac arrest, acute respiratory failure, venous thromboembolism event, ileus, surgical site infection (SSI), deep infections, urinary tract infection, nerve injury, and pneumothorax.

Statistical analysis

An a priori sample size determination was performed using an equal-variance *t*-test with a multiplicity-adjusted alpha of 0.0167 (0.05/3). It was determined that 50 subjects per group were needed in order to achieve 80% power and to detect a true effect size of 0.66 or larger. The total sample size of 110 was chosen to include 10 additional patients to protect against an estimated attrition rate of 10%. The effect size was estimated using an established minimal clinically important difference (MCID) of 2 for VAPS pain scales and a standard deviation of 3.[22]

Categorical variables were described using count and percent, whereas numerical variables are described using mean (standard deviation), median, and interquartile range. Numerical variables such as total MMEs consumed were compared between the 2 treatment arms using the Wilcoxon rank-sum test, whereas categorical variables such as sex are compared between groups using Fisher's exact test. The Kaplan-Meier method was used to plot time-to-opioid-rescue and compute the estimated event-time probabilities, whereas the log-rank test was used to compare the generated curves. The VAPS was compared between treatment arms over time using a Gaussian linear mixed model with a random intercept. All hypotheses tested were 2-sided with $P < .05$ considered statistically significant. Analysis was performed in SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 104 patients participated in the study, meeting our a priori power analysis of a minimum of 50 patients in each study arm. Eight additional patients who had been consented for the study were excluded from analysis. Four exclusions were because the patient did not receive the study medication, but rather unblinded medication. Single occurrences for exclusion were cancellation of surgery, patient decision to withdraw from the study, pre-existing opioid use with liver disease, and patient weight less than the minimum 50 kg. A Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1.

The study population consisted of 58 (55.8%) men and 46 (44.2%) women, with an average age of 69.6 years. Fifty-six (53.8%) implants were anatomic replacements, and 48 (46.2%) reverse replacements. There was no difference between the study arms for patient age, sex, patient body mass index, side of surgery, operative time, history of prior shoulder surgery, American Society of Anesthesiologists classification, and Charleston Comorbidity Index (Table II). Similarly, there was no difference between groups for the preoperative patient-reported outcomes of the Single Assessment Numeric Evaluation score, the Simple Shoulder Test, the American Shoulder and Elbow Surgeons, and the Veterans RAND 12 Item Health Survey (Table III). There were no significant adverse events as defined in the study protocol.

There was also no difference in the study groups for discharge medication ($P = .9052$). Most patients received oxycodone 5 mg tablets (57.3%), with tramadol 50 mg tablets as the next most common discharge medication (20.4%). Other medications included hydrocodone-acetaminophen 5/325 mg (13.6%), hydrocodone-acetaminophen 10/325 mg (7.8%), and oxycodone-acetaminophen 5/325 mg (1%).

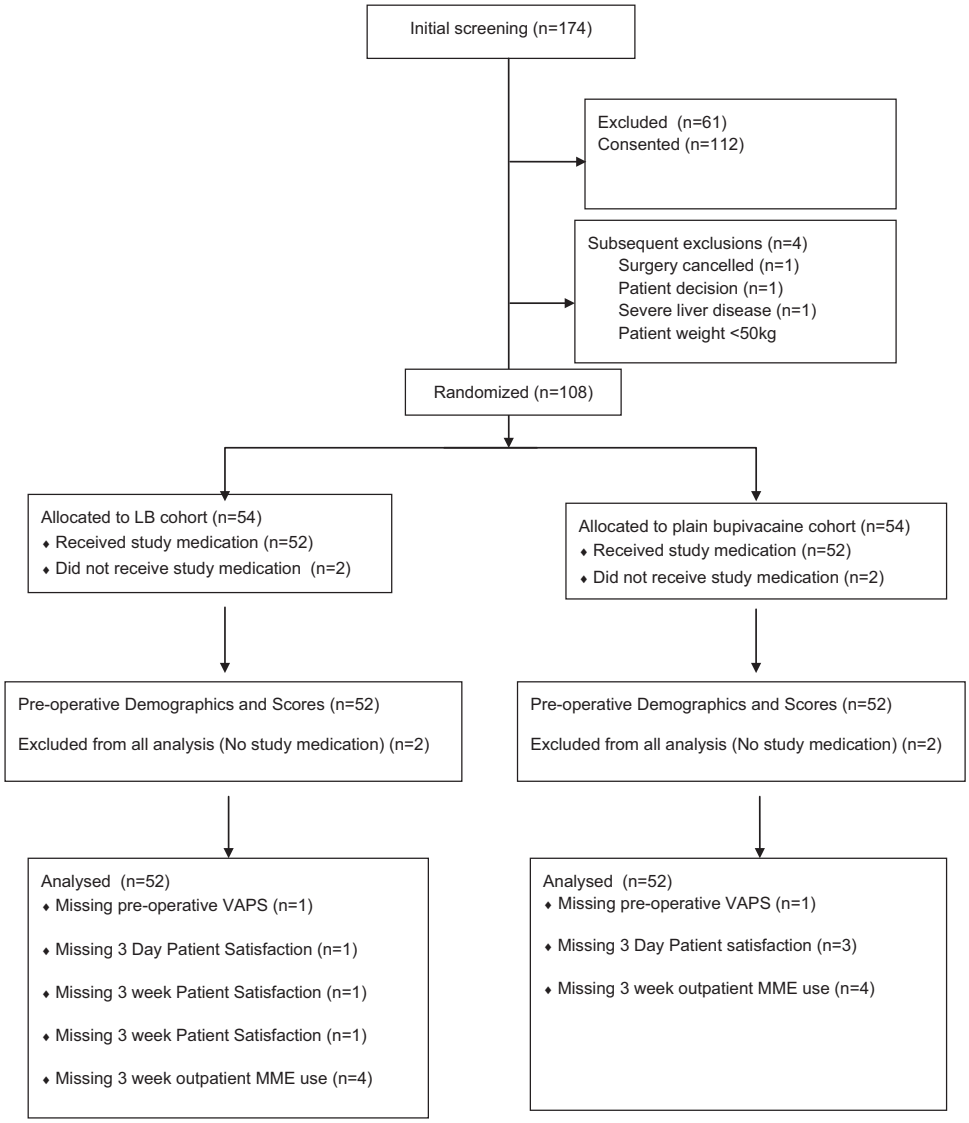

Figure 1 This Consolidated Standards of Reporting Trials flow diagram shows the allocation of patients to the study arms and subsequent follow-up. *LB*, liposomal bupivacaine; *VAPS*, visual analog pain score; *MME*, morphine milligram equivalent.

Study hypothesis 1: the average postoperative pain score over the first 72 hours will be significantly lower in the LB group

The VAPS was minimal immediately after surgery, when the interscalene block was active, worsened as the block wore off, and then gradually improved over time. This is to be expected after surgery. However, we were unable to demonstrate a substantial benefit from the use of LB over standard bupivacaine (Table IV). As pain assessment can be a rapidly changing variable, we analyzed the VAPS in multiple ways. Complying with the primary hypothesis regarding average pain scores over the first 72 hours, we found significantly less reported discomfort only on the second day after surgery with LB over standard bupivacaine. In contrast, we found a lower VAPS on the third full day home with SB. This would typically be the fourth or fifth day from surgery. However, none of these statistically significant findings for either LB or SB exceeded an MCID level of 2 for the VAPS. No significant differences were found for any of the other examined time intervals.

Study hypothesis 2: the time to block cessation will be longer in the LB group than the standard bupivacaine group

This was defined as a VAPS of 3 or greater at the surgical site and generated administration of pain medication. As the need for opioid rescue was examined, there was no apparent advantage to the use of LB over plain bupivacaine ($P = .11$ log-rank). In fact, if anything the control group

Table IV Visual analog pain scores

Variable	Total	Plain bupivacaine	Liposomal bupivacaine	*P* value
Preoperative				
Mean (SD)	5.4 (2.28)	5.4 (2.41)	5.4 (2.17)	.9273*
Median	5.5	5	6	
N	102	51	51	
First day post-surgery average				
Mean (SD)	1.7 (1.60)	1.6 (1.69)	1.8 (1.51)	.2551*
Median	1	0.9	1.8	
N	104	52	52	
Second day post-surgery average				
Mean (SD)	2.8 (2.11)	3.3 (2.22)	2.4 (1.91)	.0409*
Median	2.5	3	2	
N	104	52	52	
Third day post-surgery average				
Mean (SD)	4.6 (2.22)	5.0 (1.92)	4.2 (2.46)	.1123*
Median	5	5	4.5	
N	104	52	52	
First full day home average				
Mean (SD)	4.6 (2.27)	4.9 (2.04)	4.3 (2.45)	.1486*
Median	5	5	4.5	
N	104	52	52	
First full day home morning				
Mean (SD)	4.9 (2.71)	5.2 (2.55)	4.6 (2.84)	.2690*
Median	5	5	5	
N	104	52	52	
First full day home evening				
Mean (SD)	4.3 (2.44)	4.6 (2.40)	3.9 (2.45)	.1542*
Median	5	5	4	
N	104	52	52	
Second full day home average				
Mean (SD)	3.8 (2.25)	3.8 (1.96)	3.9 (2.53)	.8628*
Median	4	4	3.5	
N	104	52	52	
Second full day home morning				
Mean (SD)	3.9 (2.51)	3.9 (2.16)	3.9 (2.84)	.7782*
Median	4	4	3	
N	104	52	52	
Second full day home evening				
Mean (SD)	3.8 (2.43)	3.7 (2.23)	3.8 (2.64)	.9346*
Median	4	4	3.5	
N	104	52	52	
Third full day home average				
Mean (SD)	3.4 (2.32)	2.8 (1.88)	4.0 (2.57)	.0197*
Median	3	2.5	3.8	
N	104	52	52	
Third full day home morning				
Mean (SD)	3.5 (2.35)	2.9 (1.94)	4.0 (2.61)	.0429*
Median	3	3	4	
N	104	52	52	
Third full day home evening				
Mean (SD)	3.3 (2.50)	2.6 (2.06)	3.9 (2.74)	.0129*
Median	3	2	3.5	
N	104	52	52	

(*continued on next page*)

Table IV Visual analog pain scores (*continued*)

Variable	Total	Plain bupivacaine	Liposomal bupivacaine	*P* value
Week 3 postoperative				
Mean (SD)	2.1 (2.55)	2.5 (2.74)	1.7 (2.31)	.0648*
Median	1	2	1	
N	104	52	52	

SD, standard deviation.
* Wilcoxon rank sum *P* value.

trended to a longer duration before opioid rescue, but again this did not reach statistical significance (Fig. 2).

Study hypothesis 3: total opioid consumption will be lower in the LB group

There was no difference between groups in MMEs during the hospital stay, during the first 3 days after surgery, during the first 3 days home, during the first 3 weeks after discharge, or the combined inpatient and outpatient period (Table V). In the LB cohort, there was a trend for less MMEs for the first 3 days after surgery, bridging the inpatient stay and first few days home. The mean amounts of MMEs in the control group were 56.2 and 45.6 in the LB group ($P = .0584$).

Study hypothesis 4: the average patient satisfaction score regarding their pain management will be higher in the LB group

The patients' satisfaction was examined both at the third full day home and at the third week follow-up visit. Satisfaction scores were similar in both study groups (Table V). On a 0-10 scale with 10 being the highest satisfaction, the mean score was 6.9 in the control group and 6.6 in the LB arm after 3 days home ($P = .7018$). At 3 weeks, the satisfaction scores were 7.8 and 7.5, respectively ($P = .5327$).

Discussion

In this study, we found no clinical advantage to the use of LB with standard bupivacaine when compared with plain bupivacaine alone for adjunctive interscalene blocks with primary shoulder replacement. There were a few time points where one or the other preparation had some statistically significant difference. Neither of these 2 statistically significant events achieved a difference greater than the MCID for the VAPS. Recognizing that LB is designed to have a different release pattern than standard bupivacaine, it is not surprising that there was a difference in the chronology of the pain scores. The difference was just not large, rarely statistically significant, and never clinically significant. None of the other study questions including remaining pain scores, opioid usage, and patient satisfaction revealed any significant difference between the 2 study arms.

Literature on the use of LB is limited, as it is a relatively new option for medical use. Liposomal bupivacaine was initially approved by the FDA in 2011. The original indications were for bunionectomies and hemorrhoidectomies, and indications were subsequently expanded to local surgical infiltration in 2015.[30] Use in orthopedic surgery subsequently expanded, especially in the patient with total knee replacement with conflicting clinical results.[7,25] Bramlett et al[7] studied deep tissue infiltration with varying doses of LB around total knee implants. When compared with controls with plain bupivacaine, total opioid consumption, pain scores, and return to activities and work were not significantly different. In contrast, Mont et al[26] randomized patients undergoing total knee arthroplasty to periarticular block with plain bupivacaine or a mixture of bupivacaine and LB. The cohort receiving LB had improved pain scores, less opioid medication, more time to first opioid rescue, and more opioid-free patient recovery.

Recently, Abildgaard et al[2] included the work of Bramlett et al and Mont et al in a systematic review of 27 randomized controlled studies regarding the clinical efficacy of LB in orthopedic surgery. Twelve of 17 studies comparing local infiltration or periarticular block with LB demonstrated no additional benefit compared with other local anesthetics. Overall, peripheral nerve blocks without LB actually offered improved pain control and lower opioid use in the immediate postoperative period compared with blocks with LB, with no difference at subsequent time intervals.[2]

Only 1 study included in the systematic review by Abildgaard et al[2] evaluated the role of an interscalene brachial plexus block with LB in the context of shoulder surgery. Vandepitte et al[31] compared randomized patients with a standard bupivacaine interscalene block with or without the addition of LB for shoulder surgery. In addition to the relatively low power of the study with only 52 patients, the study used lower doses of plain bupivacaine than usually administered in clinical practice. In the LB arm of the study, only 5 mL of 0.25% plain bupivacaine (12.5 mg) was given with the LB as compared with the 7.5 mL of

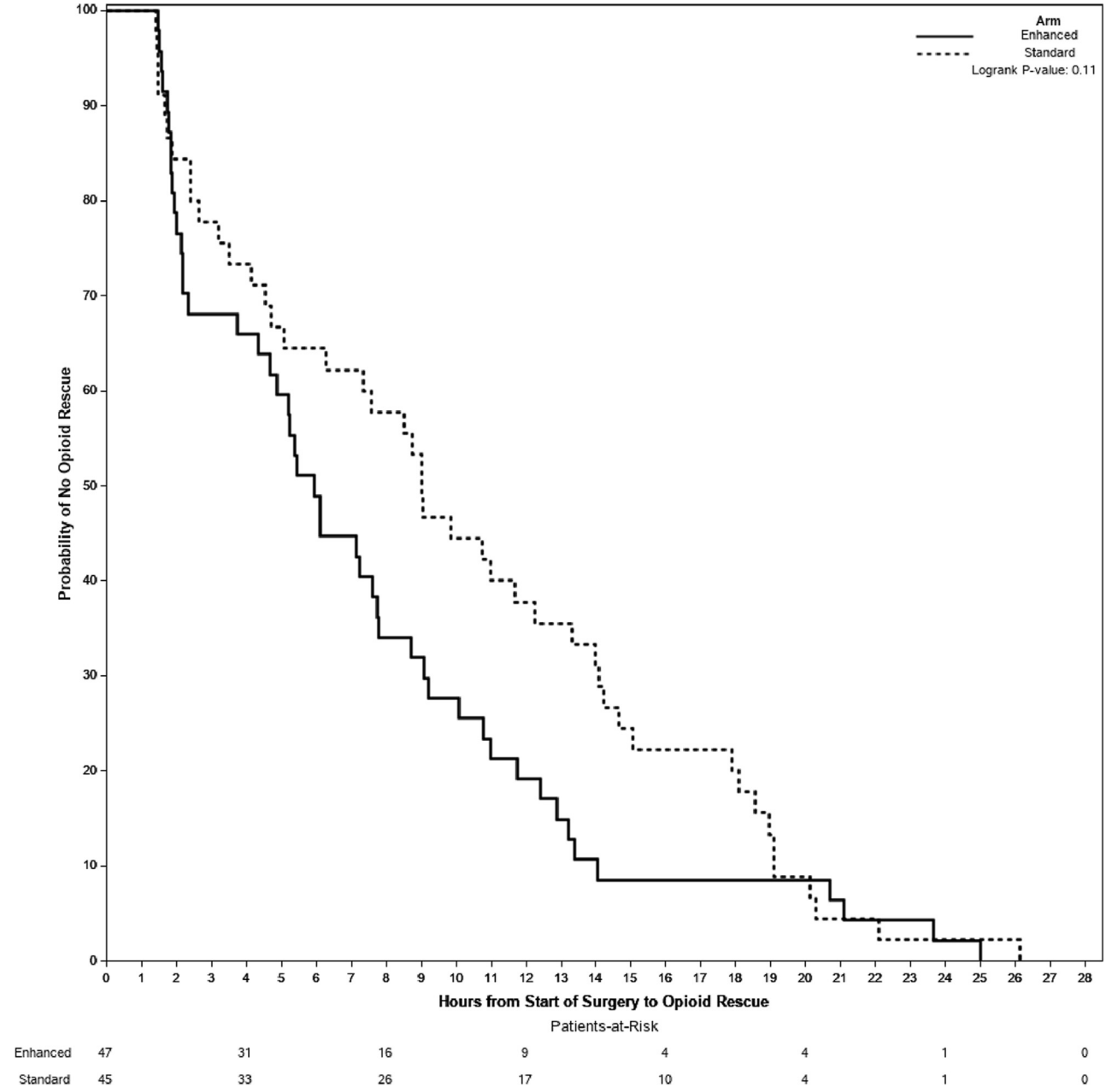

Figure 2 The probability of a patient not requiring opioid rescue at time intervals from the start of surgery. The standard arm consists of the cohort receiving only plain bupivacaine, and the enhanced group those who received liposomal bupivacaine with plain bupivacaine.

0.5% and 7.5 mL of 0.25% (56.25 mg) of plain bupivacaine mixed with LB in our study. In the plain bupivacaine arm, Vandepitte et al used 15 mL of 0.25% (37.5 mg) compared with the more typical clinical dose of 25 mL of 0.5% bupivacaine (125 mg) used in our study. Recognizing these limitations, Vandepitte et al[31] found only modest benefit for the worst pain score in the first postoperative week and for overall patient pain management satisfaction with the use of LB.

More recently, a study by Patel et al[29] compared the use of 133 mg of LB interscalene block for shoulder replacement or rotator cuff surgery with a saline block. Compared with the placebo, an LB block was found to be more effective in improved pain scores, opioid consumption, and time to opioid rescue. Again, it should be emphasized that the control for their study was saline injection.

The results of our study are consistent with the findings of Vandepitte et al[31] and Patel et al.[29] There is evidence of clinical efficacy of LB when used with plain bupivacaine for an interscalene block with shoulder replacement, on par with plain bupivacaine alone. There is just no evident superiority from the use of plain bupivacaine alone.

Table V Results

Variable	Total	Plain bupivacaine	Liposomal bupivacaine	*P* value
Pain management satisfaction third full day home				
Mean (SD)	6.8 (2.68)	6.9 (2.64)	6.6 (2.74)	.7018*
Median	7	7	7	
N	100	49	51	
Pain management satisfaction week 3				
Mean (SD)	7.6 (2.37)	7.8 (2.23)	7.5 (2.52)	.5327*
Median	8	8	8	
N	103	52	51	
MME inpatient				
Mean (SD)	32.7 (30.04)	35.6 (33.08)	29.8 (26.67)	.3673*
Median	22.5	27.5	20	
N	104	52	52	
MME total outpatient				
Mean (SD)	109.0 (106.29)	114.5 (117.92)	103.5 (94.17)	.9153*
Median	75	82.5	70	
N	96	48	48	
MME first full 3 days home				
Mean (SD)	41.4 (36.06)	43.8 (34.59)	39.0 (37.69)	.3567*
Median	30	40	30	
N	104	52	52	
MME first 72 h after surgery				
Mean (SD)	50.9 (36.72)	56.2 (35.43)	45.6 (37.55)	.0584*
Median	45	50	40.6	
N	104	52	52	
MME total				
Mean (SD)	142.4 (124.87)	150.9 (138.4)	133.9 (110.52)	.5800*
Median	103.8	111.3	100.6	
N	96	48	48	

SD, standard deviation; *MME*, morphine milligram equivalent.
* Wilcoxon rank sum *P* value.

Strengths of this study include the randomized, double-blinded protocol with appropriate power to answer the study questions. The study addresses a relevant clinical question regarding a potential increase in postoperative pain control with the use of an extended release formulation of bupivacaine (LB).

Potential limitations of the study include the possibility that it was not truly double blinded. Although every effort was made to obscure the nature of the block from the anesthetic and care teams, it would be conceivable that the anesthesiologist could detect the administered medication as it passed from the blacked-out syringe through tubing into the needle. Practically though, the attention of the anesthesiologist is directed on the proper localization of the needle via the ultrasound screen, so it is in reality highly unlikely that blinding was broken. The anesthesiologists were also not involved in data collection. VAPS and post-operative pain medication was recorded by nursing staff during the inpatient stay and gathered by the study coordinator for the outpatient period. As only the research pharmacist and the statistician at data analysis were aware of the actual medication administered, the blinded nature of the study was preserved.

To comply with hospital safety protocols for the use of LB, all patients in both study arms wore the standard wrist bracelet for patients with LB administration. This may have influenced patients' appreciation and reporting of their pain if they incorrectly felt that they had received a perceived superior medication (LB). The use of the wrist band was uniform across all patients, so this potential affect would be balanced across treatment arms.

The study protocol was based on a similar postoperative course for total shoulder arthroplasty and reverse shoulder arthroplasty, and both types of replacements were thus combined in the analysis of this study. Okoroha et al[28] have found that patients undergoing reverse shoulder arthroplasty and total shoulder arthroplasty do have similar postoperative pain profiles. In addition, there was no

significant difference in the frequency of the 2 replacement types in the treatment arms of the current study. Any variation in the replacement types in the study arms of this study should not affect the study results

Conclusion

When used for an interscalene block to provide adjunctive pain relief in shoulder replacement surgery, the addition of LB to plain bupivacaine provides no additional clinically important benefit to the patient's pain experience.

Acknowledgments

Debra L. Ryan, CCRP, Julia K. Courchaine, PA-C, MS, and Annie R. Manuel, MSN, RN, assisted with patient recruitment and data abstraction. Matthew R. Buras, MS, performed the statistical analysis.

Disclaimer

Steven J. Hattrup is a paid consultant for Zimmer-Biomet and Wright Medical Technology, Inc.; and Assistant Editor for the *Journal of Shoulder and Elbow Surgery.*

John M. Tokish receives IP royalties from, and is a paid consultant and paid presenter or speaker for Arthrex, Inc; is a board or committee member at Arthroscopy Association of North America; is a paid consultant for DePuy, A Johnson & Johnson Company; receives publishing royalties and financial or material support from and on the editorial or governing board of the *Journal of Shoulder and Elbow Surgery*; is a paid consultant and paid presenter or speaker for Mitek; and is on the editorial or governing board of *Orthopedics Today.*

David M. Rosenfeld owns stock or stock options in Aerie and Norvartis.

Lopa Misra is on the editorial or governing board of the *American Journal of Sports Medicine*; is a paid consultant and paid presenter or speaker for Arthrex; receives publishing royalties, financial, or material support from Pathology Recall; receives financial, or material support from RTI; is a paid consultant for RTI; and is a paid consultant for Cayenne.

The other authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Abdallah FW, Halpern SH, Aoyama K, Bruli R. Will the real benefits of single-shot intersclasene block please stand up? A systematic review and meta-analysis. Anesth Analg 2015;120:1114-29. https://doi.org/10.1213/ANE.0000000000000688
2. Abildgaard JT, Chung AS, Tokish JM, Hattrup SJ. Clinical efficacy of liposomal bupivacaine: a systematic review of prospective, randomized controlled trials in orthopaedic surgery. JBJS Rev 2019;7:e8. https://doi.org/10.2106/JBJS.RVW.18.00192
3. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med 2012;172:425-30. https://doi.org/10.1001/archinternmed.2011.1827
4. Al Dabbagh Z, Jansson KA, Stiller CO, Montgomery S, Weiss RJ. Long term pattern of opioid prescriptions after femoral shaft fractures. Acta Anaesthesiol Scand 2016;60:634-41. https://doi.org/10.1111/aas.12666
5. 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. https://doi.org/10.1097/ALN.0b013e31823c1030
6. Benjamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician 2008;11(Suppl):S105-20.
7. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee 2012;19:530-6. https://doi.org/10.1016/j.knee.2011.12.004
8. Brolin TJ, Cox RM, Zmistowski BM, Namdari S, Williams GR, Abboud JA. Surgeons' experience and perceived barriers with outpatient shoulder arthroplasty. J Shoulder Elbow Surg 2018;6S:S82-7. https://doi.org/10.1016/j/jse.2018.01.018
9. Brolin TJ, Mulligan RP, Azar FM, Throckmorton TW. Neer Award 2016: outpatient total shoulder arthroplasty in an ambulatory surgery center is a safe alternative to inpatient total shoulder arthroplasty in a hospital: a matched cohort study. J Shoulder Elbow Surg 2017;26:204-8. https://doi.org/10.1016/j/jse.2016.07.011
10. Cancienne JM, Brockmeier SF, Gulotta LV, Dines DM, Werner BC. Ambulatory total shoulder arthroplasty: a comprehensive analysis of current trends, complications, readmissions, and costs. J Bone Joint Surg Am 2017;99:629-37. https://doi.org/10.2106/JBJS.16.00287
11. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-8.
12. Chaudhary MA, Schoenfeld AJ, Harlow AF, Ranjit A, Scully R, Chowdhury R, et al. Incidence and predictors of opioid prescription at discharge after traumatic injury. JAMA Surg 2017;152:930-6. https://doi.org/10.1001/jamasurg.2017.1685
13. CMS. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf. Accessed August 26, 2020.
14. Efird J. Blocked randomization with randomly selected block sizes. Int J Environ Res Public Health 2011;8:15-20. https://doi.org/10.3390/ijerph8010015
15. Exparel. Available at: https://www.exparel.com/sites/default/files/PP-EX-US-5156_Nerve_Block-Anesthesia_Dosing_Guide_Aug_2019.pdf. Accessed August 26, 2020.
16. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Ther 2011;28:776-88. https://doi.org/10.1007/s12325-011-0052-y
17. Goode V, Morgan B, Muckler VC, Cary MP, Zbed C, Zychowicz M. Multimodal pain management for major joint replacement surgery. Orthop Nurs 2019;38:150-6. https://doi.org/10.1097/NOR.0000000000000525

18. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011;54: 1552-9. https://doi.org/10.1097/DCR.0b013e318232d4c1
19. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. Anesth Analg 2017;125:1733-40. https://doi.org/10.1213/ANE.0000000000002458
20. Hamilton DF, Lane JV, Gaston P, Patton JT, Macdonald D, Simpson AHRW, et al. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. BMJ Open 2013;3:e002525. https://doi.org/10.1136/bmjopen-2012-002525
21. Ilfeld BM, Vandenborne K, Duncan PW, Sessler DI, Enneking FK, Shuster JJ, et al. Ambulatory continuous interscalene nerve blocks decrease the time to discharge readiness after total shoulder arthroplasty: a randomized, triple-masked, placebo-controlled study. Anesthesiology 2006;105:999-1007. https://doi.org/10.1097/00000542-200611000-00022
22. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. J Orthop Surg Res 2015;10:24. https://doi.org/10.1186/s13018-014-0144-x
23. 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. https://doi.org/10.1002/phar.1223
24. Leroux TS, Basques BA, Frank RM, Griffin JW, Nicholson GP, Cole BJ, et al. Outpatient total shoulder arthroplasty: a population-based study comparing adverse event and readmission rates to inpatient total shoulder arthroplasty. J Shoulder Elbow Surg 2016;25:1780-6. https://doi.org/10.1016/j.jse.2016.04.006
25. Malik O, Kaye AD, Kaye A, Belani K, Urman RD. Emerging roles of liposomal bupivicaine in anesthesia practice. J Anesthethesiol Clin Pharmacol 2017;33:151-6. https://doi.org/10.4103/joacp.JOACP_375_15
26. Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: results of a randomized controlled trial. J Arthroplasty 2018;33:90-6. https://doi.org/10.1016/j.arth.2017.07.024
27. Nicholson T, Maltenfort M, Getz C, Lazaru M, Williams G, Namdari S. Multimodal pain management protocol versus patient controlled narcotic analgesia for postoperative pain control after shoulder arthroplasty. Arch Bone Jt Surg 2018;6:196-202.
28. Okoroha KR, Ratel RB, Jildeh TR, Sanchez N, Sweet MC, Rill BK, et al. Pain after anatomic total shoulder arthroplasty versus reverse shoulder arthroplasty. Orthopedics 2019;42:e247-52. https://doi.org/10.3928/01477447-20190125-01
29. Patel MA, Gadsden JC, Nedeljkovic SS, Bao X, Zeballos JL, Yu V, et al. Brachial plexus block with liposomal bupivacaine for shoulder surgery improves analgesia and reduces opioid consumption: results from a multicenter, randomized, double-blind, controlled trial. Pain Med 2020;21:387-400. https://doi.org/10.1093/pm/pnz103
30. Stundner O, Rasul R, Chui Y-L, Sun X, Madhu M, Brummett C, et al. Peripheral nerve blocks in shoulder arthroplasty: How do they influence complications and length of stay? Clin Orthop Relat Res 2014; 472:1482-8. https://doi.org/10.1007/s11999-013-3356-1
31. Vandepitte C, Kuroda M, Witvrouw R, Anne L, Bellemans J, Corten K, et al. Addition of liposome bupivacaine to bupivacaine HCl versus bupivacaine HCl alone for interscalene brachial plexus block in patients having major shoulder surgery. Reg Anesth Pain Med 2017;42:334-41. https://doi.org/10.1097/AAP.0000000000000560
32. Wells N, Pasero C, McCaffery M. Improving the quality of care through pain assessment and management. In: Hughes RG, editor. Patient safety and quality: an evidence-based handbook for nurses. Advances in patient safety. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008.
33. Wu CL, Naqibuddin M, Rowlingson AJ, Lietman SA, Jermyn RM, Fleisher LA. The effect of pain on health-related quality of life in the immediate postoperative period. Anesth Analg 2003;97:1078-85. https://doi.org/10.1213/01.ane.0000081722.09164.d5
34. Wunsch H, Wijeysundera DN, Passarella MA, Neuman MD. Opioids prescribed after low risk surgical procedures in the United States, 2004-2-12. JAMA 2016;315:1654-7. https://doi.org/10.1001/jama.2016.0130