ANESTHESIOLOGY

Interscalene Brachial Plexus Block with Liposomal Bupivacaine *versus* Standard Bupivacaine with Perineural Dexamethasone: A Noninferiority Trial

David H. Kim, M.D., Jiabin Liu, M.D., Ph.D., Jonathan C. Beathe, M.D., Yi Lin, M.D., Ph.D., Douglas S. Wetmore, M.D., Sang J. Kim, M.D., Stephen C. Haskins, M.D., Sean Garvin, M.D., Joseph A. Oxendine, M.D., Michael C. Ho, M.D., Answorth A. Allen, M.D., Marko Popovic, B.S., Ejiro Gbaje, M.P.H., Christopher L. Wu, M.D., Stavros G. Memtsoudis, M.D., Ph.D., M.B.A.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Extending the duration of interscalene nerve block reduces patient discomfort and lowers postoperative opioid consumption
- Adjuvants such as dexamethasone and liposomal formulations may prolong anesthetic action

What This Article Tells Us That Is New

- Interscalene nerve blocks using bupivacaine plus dexamethasone were compared with blocks using liposomal bupivacaine for shoulder surgery
- These alternative blocks provided very similar levels and durations of analgesia, and no differences in opioid consumption were identified
- The interscalene injection of bupivacaine plus dexamethasone and liposomal bupivacaine provide similar clinical benefits for shoulder surgery

ABSTRACT

Background: The interscalene nerve block provides analgesia for shoulder surgery. To extend block duration, provide adequate analgesia, and minimize opioid consumption, the use of adjuvants such as dexamethasone as well as the application of perineural liposomal bupivacaine have been proposed. This randomized, double-blinded, noninferiority trial hypothesized that perineural liposomal bupivacaine is noninferior to standard bupivacaine with perineural dexamethasone in respect to average pain scores in the first 72 h after surgery.

Methods: A total of 112 patients undergoing ambulatory shoulder surgery were randomized into two groups. The liposomal bupivacaine group received a 15-ml premixed admixture of 10 ml of 133 mg liposomal bupivacaine and 5 ml of 0.5% bupivacaine (n = 55), while the bupivacaine with dexamethasone group received an admixture of 15 ml of 0.5% standard bupivacaine with 4 mg dexamethasone (n = 56), respectively. The primary outcome was the average numerical rating scale pain scores at rest over 72 h. The mean difference between the two groups was compared against a noninferiority margin of 1.3. Secondary outcomes were analgesic block duration, motor and sensory resolution, opioid consumption, numerical rating scale pain scores at rest and movement on postoperative days 1 to 4 and again on postoperative day 7, patient satisfaction, readiness for postanesthesia care unit discharge, and adverse events.

Results: A liposomal bupivacaine group average numerical rating scale pain score over 72 h was not inferior to the bupivacaine with dexamethasone group (mean [SD], 2.4 [1.9] *vs.* 3.4 [1.9]; mean difference [95% CI], –1.1 [–1.8, –0.4]; $P < 0.001$ for noninferiority). There was no significant difference in duration of analgesia between the groups (26 [20, 42] h *vs.* 27 [20, 39] h; $P = 0.851$). Motor and sensory resolutions were similar in both groups: 27 (21, 48) h *versus* 27 (19, 40) h ($P = 0.436$) and 27 [21, 44] h *versus* 31 (20, 42) h ($P = 0.862$), respectively. There was no difference in opioid consumption, readiness for postanesthesia care unit discharge, or adverse events.

Conclusions: Interscalene nerve blocks with perineural liposomal bupivacaine provided effective analgesia similar to the perineural standard bupivacaine with dexamethasone. The results show that bupivacaine with dexamethasone can be used interchangeably with liposomal bupivacaine for analgesia after shoulder surgery.

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In the context of shoulder surgery, the interscalene nerve block is the most commonly used regional anesthetic technique.[1–3] Traditionally, it provides a significant analgesic benefit postoperatively. However, when used as a single-shot approach, it is limited by its duration,[4] lasting no longer

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than 24 h even when using the longer-acting local anesthetics, such as bupivacaine.[5]

At our institution, we transitioned from using standard bupivacaine to adding perineural dexamethasone as an adjuvant to prolong peripheral nerve blockade.[5] Dexamethasone is a widely used and effective adjunct that was found to increase analgesia by 6 to 8 h.[6] There have been several meta-analyses and systematic reviews,[6–8] including a Cochrane review,[9] supporting its use for upper extremity blockade.

Liposomal bupivacaine is an extended-release formulation of bupivacaine approved by the U.S. Food and Drug Administration (Silver Spring, Maryland) in 2011 for surgical site infiltration, and the transversus abdominis plane block.[10] Liposomal bupivacaine was designed to provide prolonged analgesia.[11]

Recently, the Food and Drug Administration approved its use in the interscalene nerve block.[12] However, there has been a paucity of randomized controlled trials comparing liposomal bupivacaine limiting comparisons to a placebo (saline) or "standard" bupivacaine.[13,14] A multicenter placebo-controlled trial of 140 patients demonstrated its safety and efficacy by concluding that it significantly reduced pain and opioid consumption over 48 h when compared to saline.[13] Another study including an active comparator of 52 patients suggested a "modest effect" in worst pain reduction in the first postoperative week, leading the authors to conclude that liposomal bupivacaine "may" reduce pain and enhance patient satisfaction in the first postoperative week when compared to "standard" bupivacaine.[14] It remains unclear whether the liposomal bupivacaine can significantly prolong analgesia and demonstrate superiority over an active standard bupivacaine comparator.

Given the literature suggesting that bupivacaine with perineural dexamethasone can prolong the action of peripheral nerve blocks up to 30 h,[6] we sought to compare an interscalene brachial plexus block with liposomal bupivacaine to one using standard bupivacaine with perineural dexamethasone. This study is a randomized controlled trial comparing the two injectates. Our primary hypothesis was that the average numerical rating scale pain scores over 72 h in patients given perineural liposomal bupivacaine would be noninferior to those patients given bupivacaine with perineural dexamethasone.

Materials and Methods

The Institutional Research Board of the Hospital for Special Surgery (New York, New York) approved this study, which was conducted from August 2019 to March 2021. The study was registered with ClinicalTrials.gov (NCT04047446) on July 3, 2019. A team of regional anesthesiologists considered experts by their peers in performing interscalene blocks either personally applied or supervised the blocks for all enrolled patients. A total of 112 patients scheduled for elective outpatient arthroscopic shoulder surgery were enrolled for the study. Research assistants screened patients for eligibility and upon confirmation of eligibility, one of the study investigators approached the patients in the holding area. The study rationale was explained, and if the patients were agreeable, written informed consent was obtained by one of the investigators and the research assistant.

A computerized, 1:1 ratio randomization schedule was generated by the statistician, and the group assignment was concealed from the patients and the research assistants. Pharmacists prepared concealed envelopes containing vials of 0.5% standard bupivacaine (Hospira Inc., USA) with either a vial of liposomal bupivacaine (Exparel, Pacira Inc., USA) or a vial of preservative-free dexamethasone (Fresenius Kabi AG, Germany). Upon patient arrival to the operating room, the attending anesthesiologist was unblinded and opened the sequentially numbered sealed opaque envelope to correctly mix the block injectate per study protocol. An unblinded reviewer who was otherwise unaffiliated with the study ensured that the randomization was correctly carried out. The patients remained blinded to their group assignments throughout the study.

Inclusion criteria were English-speaking patients 18 yr of age or older, with American Society of Anesthesiologists physical status I to III undergoing ambulatory arthroscopic shoulder surgery who were able to follow the study protocol. Exclusion criteria were patients with preexisting neuropathy, cervical pathologies (*i.e.*, herniated disc, myelopathy), chronic pain syndromes (defined as reflex sympathetic dystrophy or complex regional pain syndrome), history of allergy to a local anesthetic or one of the study medications, severe respiratory conditions, psychiatric or cognitive disorders that prohibit patients from adhering to the study protocol, history of drug or alcohol abuse, chronic opioid use (longer than 3 months or daily morphine equivalents more than 5 mg/day for 1 month), contraindication for general anesthesia and/or interscalene nerve block, pregnancy, and planned open shoulder arthrotomies.

The primary outcome was defined as the average numerical rating scale pain score at rest over 72 h (average of three 24-h time points: 24, 48, and 72 h). Secondary outcomes included numerical rating scale pain scores at rest at each time points (24, 48, 72, 96, and 168 h after time of block placement); numerical rating scale pain scores with movement; Brief Pain Inventory short form; opioid consumption; and patient satisfaction with pain treatment in the postanesthesia care unit (PACU) and on postoperative days 1, 2, 3, 4, and 7. Additionally, duration of the analgesic block, sensory block, and motor block resolution were assessed by the research assistant through a scripted telephone interview at 24, 48, and 72 h after the block placement (or longer, if block continues; Supplemental Digital Content 1, http://links.lww.com/ALN/C767). Success of the interscalene block, adverse effects of the interscalene block, incidence of interscalene block–related side effects, time to readiness for postanesthesia care unit (PACU)

discharge, and length of PACU stay were also measured and included as secondary outcomes.

The Brief Pain Inventory (short form) is a widely used, validated, self-administered questionnaire that evaluates pain severity and the impact of pain on daily function (pain interference).[15] It has been used as an internally reliable, consistent method to assess for daily pain intensity and pain interference.[16] The questionnaire assesses pain severity by asking for worst pain, least pain, average pain, and pain now (using a scale of 0 to 10, with 10 being the worst pain). It evaluates how pain interferes with general activity, mood, walking, working, relationships, sleep, and enjoyment in life (using a scale of 0 to 10, 10 being complete interference). Each patient was given the Brief Pain Inventory short form on discharge and reported the scores to the research assistants during the postoperative phone interviews. Because numerical rating scale pain scores at rest and movement were used, we calculated only the pain interference mean scores, using a minimally clinically relevant difference of 2.1.[17]

All clinical and nonclinical members involved with patient care and study data collection/data analysis including the surgeons, operating room and PACU nurses, research assistants, and statisticians were blinded to the group assignment. Only the attending anesthesiologists performing the block were not blinded to correctly mix the study block injectate. All patients were discharged on the day of surgery with a brace. The study was conducted in accordance with the original protocol, and no changes were made to the eligibility criteria during the trial. All study data were recorded in a secure REDCap database using a hospital-issued password-protected device. The trial was done at a single institution, the Hospital for Special Surgery (New York, New York). An interim analysis of just unanticipated admissions (not primary or secondary outcomes analysis) was performed by a separate statistician not involved with the study at 50% enrollment to ensure patients in either bupivacaine with dexamethasone or liposomal bupivacaine group were not being admitted or readmitted for pain control or respiratory distress at different rates. Before patient enrollment, an agreement was made to stop the study early if over 30% of patients were being admitted. Our interim analysis showed no admissions or readmissions for block-related side effects. The full trial protocol is available upon request.

Baseline Measurements

Per institutional policy, a surgical physician assistant performed a sensory (*e.g.*, intact sensation to light touch) and motor strength exam (scale from 0 to 5) on the operative extremity in the holding area before surgery. Patients with abnormal baseline exams and history of reflex sympathetic dystrophy and/or chronic regional pain syndrome were not eligible for the study and were not approached. If eligible, the research assistants approached the patients and collected their demographics data.

Interscalene Nerve Block

All enrolled patients had their interscalene blocks performed in the operating room with sedation (2 to 5 mg intravenous midazolam). The block was performed under sterile conditions. Using a high-frequency linear ultrasound transducer (SonoSite M-Turbo, USA), the cervical roots and interscalene muscles were identified. The anesthesiologist inserted a 22-gauge 2 3/8-inch Chiba needle (Havel's Incorporated, USA), lateral to medial, with an in-plane technique into the interscalene groove. Once the tip of the needle was positioned in between the C5 and C6 nerve roots, the study injectate of either a 15-ml admixture of 10 ml of 133 mg liposomal bupivacaine and 5 ml of 0.5% bupivacaine was deposited for the liposomal bupivacaine group or a 15-ml admixture of 15 ml of 0.5% bupivacaine with 4 mg of preservative-free dexamethasone was deposited for the bupivacaine with dexamethasone group. Of note, the total dose of bupivacaine in the perineural liposomal bupivacaine group is higher (133 mg liposomal bupivacaine + 25 mg standard bupivacaine) than the comparator, bupivacaine with dexamethasone group (75 mg standard bupivacaine.). Each anesthesia record was audited by a blinded research assistant not involved in patient enrollment or postoperative assessment for anesthetic deviations (*e.g.*, different mixture of study injectate or rescue blocks performed either intraoperatively or postoperatively), and none were found.

Intraoperative Management

After block induction, general anesthesia was induced by administration of propofol (induction doses of 2 mg/kg) by the attending anesthesiologist. Laryngeal mask airway was inserted, and anesthesia was maintained with propofol infusion and fentanyl (25 to 50 μg titrated up to 200 μg) as needed. To avoid postoperative nausea and vomiting, 4 mg dexamethasone (bupivaciane with dexamethasone group) or 8 mg dexamethasone (liposomal bupivacaine group) was administered, as well as 4 mg ondansetron for both groups. Before the end of surgery, 15 to 30 mg ketorolac were also given (30 mg for patients under 65 and over 50 kg and 15 mg for patients under 65 or under 50 kg). The surgeons injected 5 to 10 ml of local anesthetic at the posterior portal site usually not covered by the interscalene block.

Postoperative Analgesics

Postoperative medications included acetaminophen (1 g IV upon PACU arrival or 750 mg if less than 50 kg), ketorolac (30 mg IV every 6 h after the intraoperative dose if not yet discharged or 15 mg for 65 yr or older or less than 50 kg). For pain control, the following order set was utilized: 50 mg tramadol every 6 h as needed (mild pain, 1 to 3 on the numerical rating scale); 100 mg tramadol every 6 h as needed (or 75 mg if less than 50 kg; moderate pain, 4 to 6 on the numerical rating scale); 5 mg oxycodone every 3 h as

needed (severe pain, 7 to 10 on the numerical rating scale); and 0.5 mg hydromorphone IV every 15 min as needed, up to 1 mg, for rescue analgesia. Patients were discharged with naproxen (500 mg every 12 h), oxycodone–acetaminophen (5 to 325 mg, 1 or 2 tabs every 4 h as needed), and ondansetron (8 mg every 8 h as needed).

Recovery Room Assessment

The extent of sensory and motor block over time was evaluated in all patients by alcohol swab (sensory) test and handgrip strength (motor exam) after arrival in the PACU by the research assistant and an anesthesiologist who was blinded to the group assignment. Time to readiness for PACU discharge was evaluated every 15 min using the Post Anesthetic Discharge Scoring System, as well as the total length of PACU stay as defined by time of PACU admission to PACU discharge.

Adverse Effects

In the PACU, patients were assessed for interscalene-related side effects, which included the presence of Horner's syndrome, hoarseness, dyspnea, and singultus. Neuropraxia or postoperative neurologic symptoms, as defined by persistent numbness, tingling, and/or weakness of the operative extremity was assessed at 1 week into the postoperative period. If present, the attending anesthesiologist was notified, and the patient was assessed again on postoperative day 14 with continual follow-up until postoperative neurologic symptom resolution.

Numerical Rating Scale Pain, Brief Pain Inventory, and Block Duration

Numerical rating scale pain scores at rest were recorded every 30 min, and total opioid consumption was documented when patients were discharged from the PACU. As aforementioned, self-reported numerical rating scale pain scores at rest and movement, Brief Pain Inventory (short form) questionnaire, opioid consumption, satisfaction with pain treatment, duration of the block, sensory, and motor block resolution were assessed and determined by the research assistant on postoperative days 1 to 4 and on day 7 *via* scripted telephone interview. Time to first analgesic medication usage upon discharge was also asked *via* scripted questionnaire by the research assistant.

Statistical Analysis

Because there have been several reported trials comparing infiltrative liposomal bupivacaine with periarticular injections containing bupivacaine and adjuvants showing no superiority in the orthopedic literature,[18,19] we decided to perform a noninferiority study on perineural liposomal bupivacaine with bupivacaine with perineural dexamethasone. The sample size was determined with the aim to reject the inferiority of liposomal bupivacaine compared to bupivacaine with dexamethasone. A previous arthroscopic shoulder trial comparing two different regional techniques defined a mean difference for numerical rating scale at rest of less than 1.3[20,21] to be considered noninferior. Based on data from a study completed at our institution,[22] we assumed that the numerical rating score mean difference between liposomal bupivacaine and bupivacaine with dexamethasone is 0.8 with a SD of 1. Using these estimates, a sample size of 51 for each group ($\alpha = 0.05$, power = 0.8) was required. To account for attrition, a total of 112 patients were included in the final sample (10% additional).

Missing values for the primary outcome, numerical rating scale at rest at 24, 48, and 72 postoperative hours, were imputed with the median for each respective time point. An average of numerical rating scale at rest scores at 24, 48, and 72 postoperative hours (postoperative days 1 to 3) was calculated to serve as the primary outcome. Standardized differences were used to make balance comparisons. If the absolute value of the standardized difference for a factor was greater than $1.96 \times \sqrt{(\frac{2}{56})} = 0.37$, it was considered as evidence of imbalance for that factor.[23] This study used an intention-to-treat basis. Depending on the data's distribution, descriptive statistics for continuous variables were presented as either mean (SD) or median (interquartile range). Normality of continuous variables was assessed using Shapiro–Wilk tests. A one-sided two-sample *t* test with a noninferiority margin of 1.3 points was run to determine whether the liposomal bupivacaine group's numerical rating scale at rest from 24 to 72 postoperative hours was noninferior to that of the bupivacaine with dexamethasone group at the α level of 0.05. For sensitivity analysis, a one-sided two sample test with nonimputed primary outcome data was also run. Secondary continuous outcomes measured at one time point were analyzed using two-sample *t* tests or Wilcoxon rank sum tests for nonnormal variables. Categorical variables were analyzed using chi-square or Fisher's exact tests. Continuous secondary outcomes measured at multiple time points were analyzed using linear mixed models with a generalized linear mixed model approach that included a group by time interaction. Covariance structures for linear mixed models were determined by assessing the Akaike's Information Criteria/Bayesian Information Criteria statistics. For the linear mixed numerical rating scale at rest model, an autoregressive covariance structure was used with clustering on record identification (generated from randomization). The model applied restricted maximum likelihood, as well as a model-based fixed effects standard error method, and a group by time interaction was included. All secondary analyses were considered to be exploratory. They were not adjusted for multiple testing and should be interpreted carefully. Blinding success in each treatment group was assessed using Bang's blinding index.[24] Statistical procedures were performed using SAS version 9.4 (SAS Institute, USA).

An interim analysis was performed at the 50% mark of enrollment to ensure that neither group was leading to unanticipated admissions for pain control or respiratory distress. The primary outcome and other secondary outcomes were not analyzed and kept "blinded." A blinded statistician not involved in the study was asked to look only at the number of admissions in either group. The statistician confirmed that neither group had greater than 30% admissions, and we continued enrollment.

Results

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patient randomization and exclusion is presented in figure 1. A total of 112 patients were enrolled in the study, with 56 in each group. One patient in the liposomal bupivacaine group was excluded from the study before opening the concealed envelope. The patient was deemed ineligible because the surgeon changed the procedure after reviewing images. The procedure was changed from an arthroscopic shoulder surgery to an open shoulder procedure that included obtaining a graft from a lower extremity. There were no significant differences in baseline demographic characteristics between the liposomal bupivacaine group and the bupivacaine with dexamethasone group (table 1).

Primary Outcome (Average Numerical Rating Scale Pain Score over 3 Days)

Average numerical rating scale pain score over 3 days postoperatively for the liposomal bupivacaine group was noninferior to the bupivacaine with dexamethasone group (2.4 [1.9] *vs.* 3.4 [1.9], –1.1 [–1.8, –0.4]; $P < 0.001$ for noninferiority; table 2). Imputation with the median was done to account for missing observations (1 missing liposomal bupivacaine observation at 24 h, 3 missing liposomal bupivacaine and 1 missing bupivacaine with perineural dexamethasone at 48 h, and 4 missing liposomal bupivacaine and 3 missing bupivacaine with perineural dexamethasone at 72 h). A sensitivity analysis (nonimputed primary outcome) was performed, and the results were consistent with the imputed primary outcome above (–1.1 [–1.9, –0.4]; $P < 0.001$). In addition, based on a manuscript peer reviewer request for superiority testing *via post hoc* analysis, superiority testing (two-tailed two-sample *t* test) was performed and found that the average numerical rating scale pain score over 72 h postoperatively was statistically significantly lower for the liposomal bupivacaine group compared to the bupivacaine with dexamethasone group ($P = 0.002$). However, the mean average numerical rating scale pain score over 72 h difference was 1.1, which is below the predetermined clinically meaningful margin of 1.3.

Numerical Rating Scale Pain Scores

Numerical rating scale pain scores at rest were lower in the liposomal bupivacaine group on postoperative days 1, 2, and 3 with statistical significance ($P = 0.025$, <0.001, and 0.028; table 2). Numerical rating scale pain scores on movement were lower in the liposomal bupivacaine group on postoperative days 2 and 3 with statistical significance ($P = 0.025$ and 0.041; table 2). Although several time points demonstrated statistically significant differences, there was none in the mean difference between the liposomal bupivacaine group and bupivacaine with dexamethasone's group that reached clinical relevance (using the study's *a priori* clinical relevance of 1.3) at rest and on movement (–1.5 and –1.4; fig. 2A).

Brief Pain Inventory (Short Form)

Brief Pain Inventory data showed that on postoperative days 2, 3, and 4, the liposomal bupivacaine group was found to have statistically significant lower average pain interference scores ($P = 0.035$, 0.014, and 0.043; table 3). While there was a statistically significant difference between the groups at some time points, Brief Pain Inventory scores did not reach clinical significance at any time point (using the study's *a priori* clinical relevance of 2.1; fig. 2B).

Opioid Consumption

There was no difference in opioid consumption between groups at any time points: PACU, postoperative days 1 to 4 and 7 ($P = 0.942$, 0.102, 0.110, 0.116, 0.549, and 0.599, respectively; table 4), including intraoperatively ($P = 0.090$; table 4; fig. 3).

Block Duration

There was no significant difference in block duration between the liposomal bupivacaine and bupivacaine with perineural dexamethasone groups as measured by analgesic duration (26 [20, 42] h *vs.* 27 [20, 39] h; $P = 0.851$; table 5). There was also no difference between groups for sensory (27 [21, 44] h *vs.* 31 [20, 42] h; $P = 0.862$) and motor block resolution (27 [21, 48] h *vs.* 27 [19, 40] h; $P = 0.436$).

Patient Satisfaction

Patient satisfaction was higher in the bupivacaine with the dexamethasone group in the PACU (9.8 *vs.* 9.4, $P = 0.032$; table 6). There was no difference between groups at any other time point (fig. 4). Patient satisfaction was not clinically significantly different at any time point.

Block Success, Readiness for PACU Discharge/Length of Stay, Adverse Events, Interscalene Block–related Side Effects

There was no clinically significant difference in block success, readiness for PACU discharge, and PACU length of stay (table 7). At postoperative day 7, there were no statistically significant difference between groups (6 *vs.* 3, $P = 0.483$) when assessing for postoperative neurologic symptoms. On

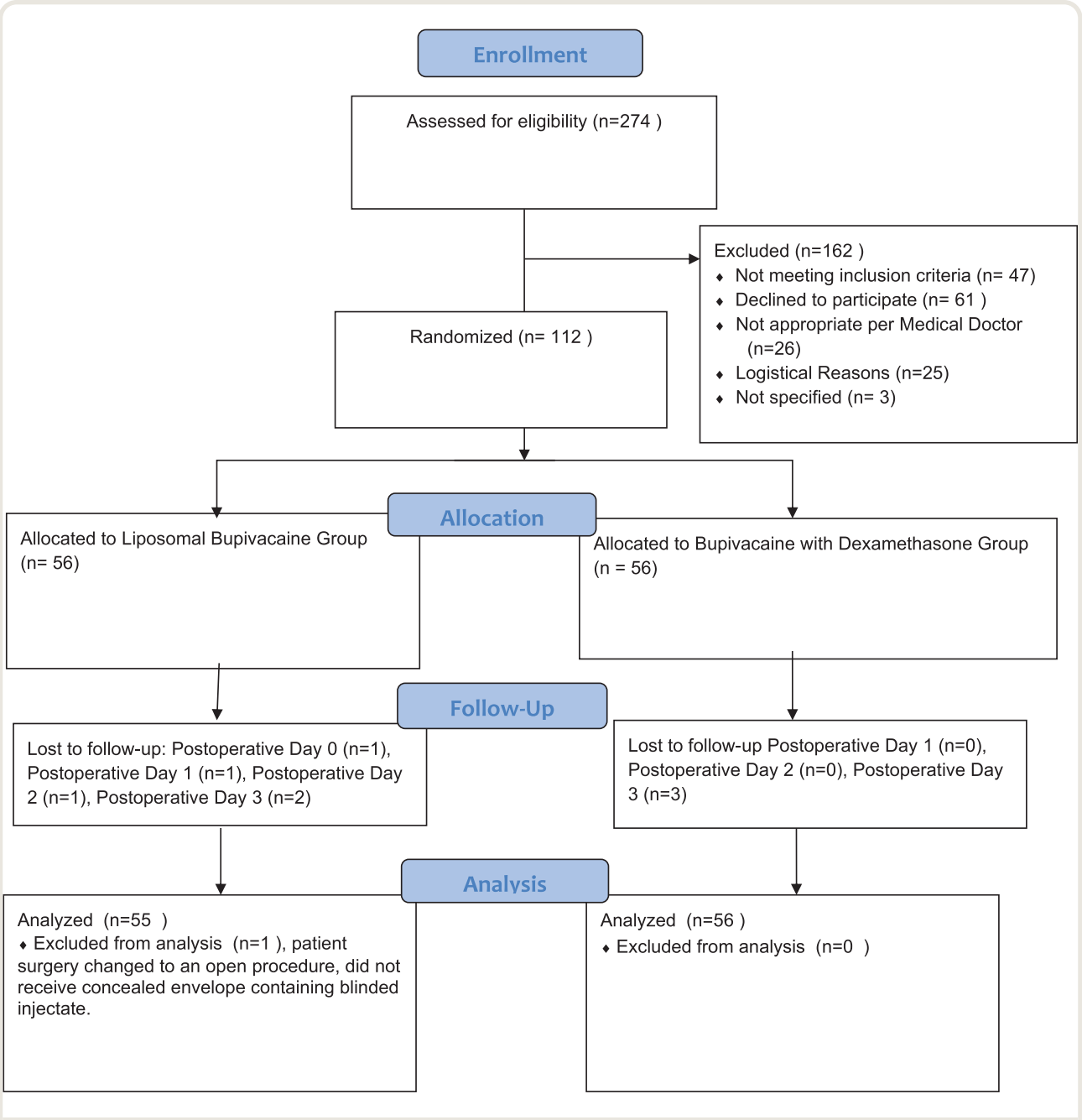

Fig. 1. Liposomal bupivacaine Consolidated Standards of Reporting Trials flow.

follow-up, no patients had postoperative neurologic symptoms on postoperative day 14. There were more cases of hoarseness on postoperative day 1 in the liposomal bupivacaine group (25 *vs.* 14; $P = 0.014$).

Discussion

Our study is a randomized controlled trial to compare perineural liposomal bupivacaine to bupivacaine with adjuvant perineural dexamethasone for use in interscalene nerve blocks in patients undergoing ambulatory arthroscopic shoulder surgery on postoperative pain. Our study demonstrated that the liposomal bupivacaine's average numerical rating scale pain score over 3 days is noninferior to the bupivacaine with dexamethasone group. We demonstrated a duration similar to a standard bupivacaine with perineural dexamethasone block (30 h) but did not support the proposed 48 to 72 h as once purported in earlier literature.[11] There was no difference between groups for analgesic duration, motor/sensory resolution, and opioid consumption,

Table 1. Patient Characteristics and Demographics

Characteristic	Liposomal Bupivacaine (n = 55)	Bupivacaine with Dexamethasone (n = 56)	Standardized Difference*
Age, yr (median [interquartile range])	55 (48, 61)	49 (39, 63)	0.337
Height, cm (median [interquartile range])	175 (168, 183)	178 (170, 183)	–0.191
Weight, kg (mean [SD])	84.8 (16.5)	85.8 (15.8)	–0.027
Body mass index, kg/m^2 (mean [SD])	27.6 (41)	27.5 (4.1)	0.033
Race, n (%)			0.067
Asian	2 (3.6)	3 (5.4)	
White	45 (81.8)	46 (82.1)	
Black	5 (9.1)	5 (8.9)	
Unknown	3 (5.5)	2 (3.6)	
Ethnicity, n (%)			0.193
Hispanic	2 (3.6)	4 (7.1)	
Non-Hispanic	52 (94.6)	52 (92.9)	
Unknown	1 (1.8)	0 (0)	
ASA status (I/II), n	10/45	12/44	–0.082
Sex			–0.197
Male, n (%)	43 (78.2)	48 (85.7)	
Female, n (%)	12 (21.8)	8 (14.3)	

*Imbalance was defined as a standardized difference above the threshold of $1.96 \times \sqrt{(\frac{2}{56})} = 0.37$.[23]
ASA, American Society of Anesthesiologists.

Table 2. Numerical Rating Scale Pain Scores

Time	Numerical Rating Scale Score, Mean (SD)		Difference in Means, Liposomal – Dexamethasone (95% CI)	*P* Value
	Liposomal Bupivacaine	Bupivacaine with Dexamethasone		
Average at rest				
Postoperative days 1 to 3*	2.4 (1.9)	3.4 (1.9)	–1.1 (–1.8, –0.4)	< 0.001
At rest				
In postanesthesia care unit at 60 min	1.3 (1.9)	0.9 (1.8)	0.4 (–0.4, 1.2)	0.351
Postoperative day 1	2.1 (2.6)	3 (2.5)	–0.9 (–1.7, –0.1)	0.025
Postoperative day 2	2.5 (2.3)	4.1 (2.7)	–1.5 (–2.3, –0.7)	< 0.001
Postoperative day 3	2.4 (2.2)	3.3 (2.4)	–0.9 (–1.7, –0.1)	0.028
Postoperative day 4	2.5 (2.0)	3.0 (2.2)	–0.5 (–1.4, 0.4)	0.242
Postoperative day 7	1.7 (2.0)	2.3 (2.2)	–0.5 (–1.4, 0.4)	0.245
With movement				
Postoperative day 1	4 (3.1)	4.3 (3.1)	–0.3 (–1.6, 1.0)	0.676
Postoperative day 2	4.1 (2.9)	5.6 (3.1)	–1.4 (–2.6, –0.2)	0.025
Postoperative day 3	4 (2.7)	5.3 (2.3)	–1.2 (–2.4, –0.1)	0.041
Postoperative day 4	4.0 (2.8)	4.9 (2.4)	–0.8 (–2.0, 0.4)	0.199
Postoperative day 7	3.9 (2.6)	4.7 (2.5)	–0.7 (–2.0, 0.6)	0.272

*A noninferiority *t* test was conducted with noninferiority margin of 1.3 points and an α level of 0.05. The missing values imputed with the median. A sensitivity analysis without imputed values was run, and the results were consistent with the results from the imputed data.

respectively. Both groups were able to achieve prolonged analgesia (over 24 h).

Our study represents a randomized controlled trial using an active comparator in the form of an adjuvant that has been proven to effectively prolong analgesia (*i.e.*, dexamethasone). Perineural dexamethasone is a commonly used additive to prolong the duration of analgesia for brachial plexus block, and the analgesic efficacy of dexamethasone is well established.[6–9] Although not definitive, it does appear that perineural dexamethasone combined with bupivacaine prolongs the duration of analgesia slightly longer than that seen with compared with systemic dexamethasone for peripheral nerve block.[25–27] Although we believe our study is one of the few randomized controlled trials to compare perineural liposomal bupivacaine to the adjuvant perineural dexamethasone for use in interscalene nerve blocks, there is only one published active comparator randomized controlled trial investigating perineural liposomal bupivacaine[14] use in interscalene nerve blocks. That study found a significant difference in lower Brief

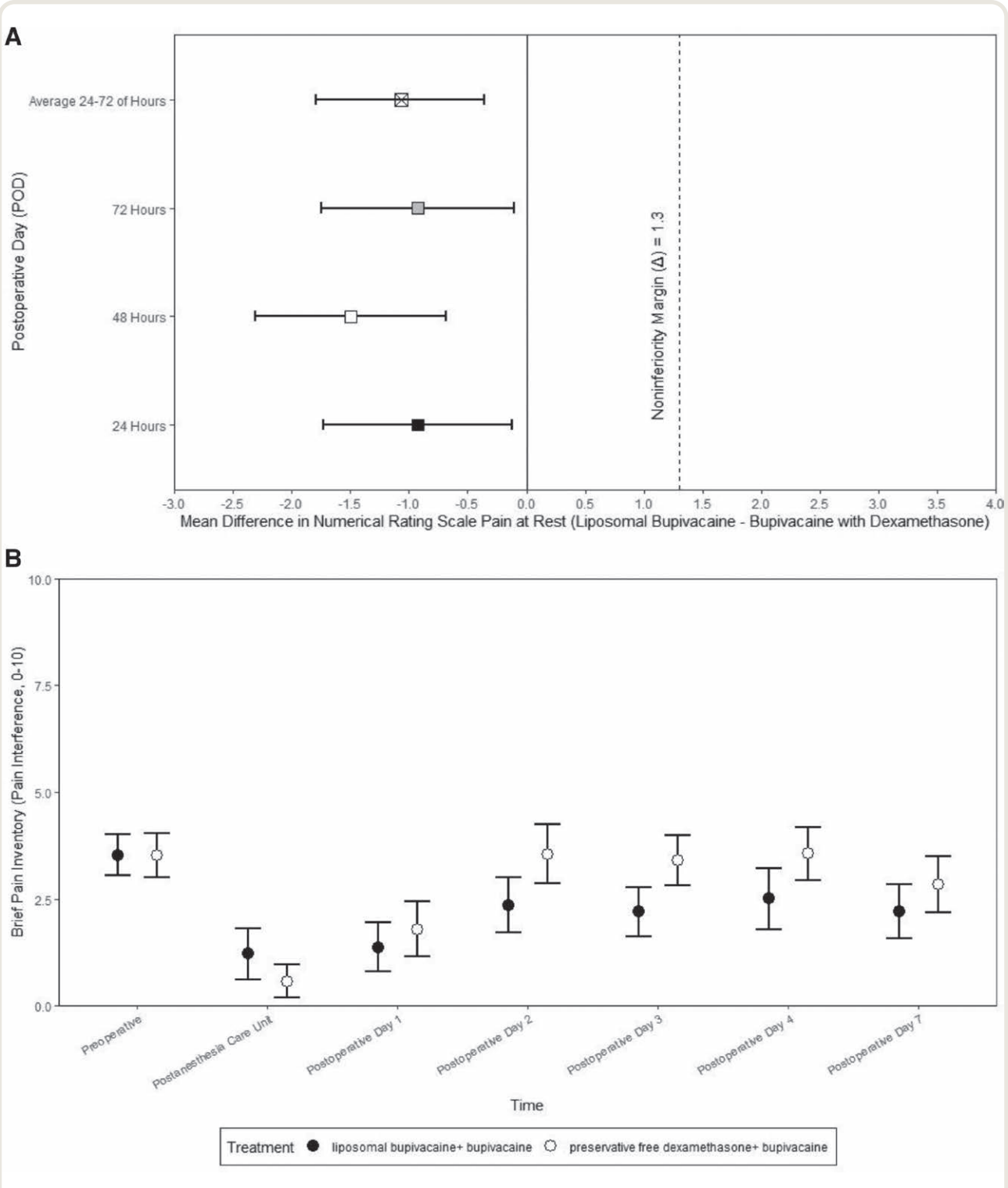

Fig. 2. (*A*) Mean differences of numerical rating scale at rest. The data are plotted as means ± 95% CI. (*B*) Brief Pain Inventory Pain score (Pain Interference) over time. The data are plotted as means ± 95% CI for each randomization group over time.

Pain Inventory scores over a period of 1 week; however, there were no mean difference calculations provided to assess for clinical relevance.

We designed our study to compare perineural liposomal bupivacaine to the adjuvant perineural dexamethasone for use in interscalene nerve blocks and for clinical relevance.

Table 3. Brief Pain Inventory Short Form: Pain Interference Scores

Time	Numerical Rating Scale Score, Mean (SD)		Difference in Means, Liposomal – Dexamethasone (95% CI)	*P* Value
	Liposomal Bupivacaine	Bupivacaine with Dexamethasone		
Preoperative	3.6 (1.8)	3.5 (1.9)	0.1 (–0.6, 0.7)	0.884
Postanesthesia care unit	1.2 (2.0)	0.6 (1.4)	0.6 (–0.1, 1.3)	0.077
Postoperative day 1	1.4 (2.0)	1.8 (2.3)	–0.4 (–1.3, 0.4)	0.296
Postoperative day 2	2.4 (2.3)	3.6 (2.5)	–1.0 (–1.9, –0.1)	0.035
Postoperative day 3	2.2 (2.0)	3.4 (2.1)	–1.0 (–1.8, –0.2)	0.014
Postoperative day 4	2.5 (2.3)	3.6 (2.1)	–0.9 (–1.8, –0)	0.043
Postoperative day 7	2.2 (2.1)	2.9 (2.1)	–0.5 (–1.3, 0.3)	0.240

Table 4. Opioid Consumption

Time	Oral Morphine Equivalents (mg)			
	Mean (SD)		Difference in Means, Liposomal – Dexamethasone (95% CI)	*P* Value
	Liposomal Bupivacaine	Bupivacaine with Dexamethasone		
Postanesthesia care unit	1.8 (4.5)	1.7 (4.6)	0.1 (–1.6, 1.8)	0.942
Postoperative day 1	4.8 (8.6)	8.1 (10.4)	–3.0 (–6.7, 0.6)	0.102
Postoperative day 2	12.3 (15.6)	18.2 (20.8)	–5.7 (–12.6, 1.2)	0.110
Postoperative day 3	8.9 (12.5)	13.2 (14.0)	–4.0 (–9.0, 1.0)	0.116
Postoperative day 4	6.9 (13.8)	9.7 (15.5)	–1.8 (–7.5, 4.0)	0.549
Postoperative day 7	3.7 (7.4)	3.3 (7.2)	0.8 (–2.2, 3.8)	0.599
Intraoperative, median (quartile 1, quartile 3)	28.3 (15.0, 30.0)	23.2 (7.5, 30.0)		0.090*

*The *P* value for intraoperative opioid consumption was determined by Wilcoxon rank sum test.

Table 5. Analgesic Block Duration, Sensory Resolution, and Motor Block Resolution

Evaluation Question	Time (Median [Quartile 1, Quartile 3]), h		Wilcoxon Rank Sum Test *P* Value
	Liposomal Bupivacaine	Bupivacaine with Dexamethasone	
When did your pain relief from the block completely wear off?	26 (20, 42)	27 (20, 39)	0.851
Sensory Resolution: When did your numbness completely resolve and return to normal?	27 (21, 44)	31 (20, 42)	0.862
Motor Block Resolution: When did your arm or hand weakness resolve and return to normal?	27 (21, 48)	27 (19, 40)	0.436

Table 6. Patient Satisfaction

Time	Patient Satisfaction Score, Mean (SD)		Difference in Means, Liposomal – Dexamethasone (95% CI)	*P* Value
	Liposomal Bupivacaine	Bupivacaine with Dexamethasone		
Postanesthesia care unit	9.4 (1.3)	9.8 (0.5)	–0.4 (–0.8, 0)	0.032
Postoperative day 1	9.3 (1.4)	9.2 (1.6)	0.2 (–0.4, 0.7)	0.597
Postoperative day 2	8.9 (2.1)	8.6 (1.8)	0.3 (–0.5, 1.0)	0.497
Postoperative day 3	9.2 (1.4)	8.6 (1.7)	0.6 (–0.1, 1.1)	0.084
Postoperative day 4	9.1 (1.2)	8.5 (1.7)	0.4 (–0.2, 1.0)	0.215
Postoperative day 7	9.1 (1.5)	8.4 (2.1)	0.6 (–0.1, 1.3)	0.111

Table 7. Postoperative Neurologic Symptoms, Postanesthesia Care Unit Discharge, and Interscalene Block–related Side Effects

Characteristic	Liposomal Bupivacaine	Bupivacaine with Dexamethasone	*P* Value
Postoperative neurologic symptoms			
Postoperative day 7, n (%)	6 (14.0)	3 (7.1)	0.483
Postoperative day 14, n (%)	0	0	Not applicable
Time to readiness for discharge, min (median [quartile 1, quartile 3])	90 (60, 119)	90 (75, 119)	0.413
Postanesthesia care unit length of stay, min (median [quartile 1, quartile 3])	163.5 (138, 197)	163 (145, 197)	0.876
Interscalene block–related side effects (Horner's syndrome), n (%)			
Postanesthesia care unit	5 (10.0)	5 (9.4)	> 0.999
Hoarseness			
Postanesthesia care unit	10 (20.8)	12 (22.2)	0.865
Postoperative day 1	25 (50.0)	14 (26.4)	0.014
Postoperative day 2	10 (20.4)	6 (11.8)	0.239
Postoperative day 3	5 (10.4)	9 (17.3)	0.321
Postoperative day 4	3 (7.0)	5 (10.2)	0.719
Postoperative day 7	2 (4.7)	2 (4.8)	> 0.999
Hiccups			
Postanesthesia care unit	0	0	Not applicable
Postoperative day 1	5 (10.0)	3 (5.7)	0.480
Postoperative day 2	0	2 (3.9)	0.495
Postoperative day 3	2 (4.2)	0	0.233
Postoperative day 4	2 (4.7)	0	0.221
Postoperative day 7	1 (2.3)	1 (2.4)	> 0.999
Coughing			
Postanesthesia care unit	3 (6.3)	4 (7.6)	> 0.999
Postoperative day 1	6 (12.0)	8 (15.1)	0.647
Postoperative day 2	4 (8.2)	7 (13.7)	0.379
Postoperative day 3	3 (6.3)	6 (11.5)	0.491
Postoperative day 4	6 (14.0)	4 (8.3)	0.508
Postoperative day 7	1 (2.3)	5 (11.9)	0.110
Dyspnea			
Postanesthesia care unit	4 (8.5)	3 (5.6)	0.702
Postoperative day 1	7 (14.0)	7 (13.2)	0.907
Postoperative day 2	3 (6.1)	2 (3.9)	0.675
Postoperative day 3	2 (4.2)	4 (7.7)	0.679
Postoperative day 4	2 (4.7)	3 (6.1)	> 0.999
Postoperative day 7	1 (2.3)	1 (2.4)	0.506

Because there have been multiple published studies comparing liposomal bupivacaine to plain bupivacaine[28–30] but none to plain bupivacaine with dexamethasone, we felt that a randomized controlled trial comparing perineural liposomal bupivacaine to plain bupivacaine with the adjuvant perineural dexamethasone for interscalene nerve blocks would be clinically relevant for many practitioners. The perineural analgesic efficacy of dexamethasone has already been noted previously, and a survey sent to all members of the Society for Ambulatory Anesthesia (SAMBA; Milwaukee, Wisconsin) noted that for patients receiving nerve block, 85% of respondents discharged patients with long-acting blocks.[31] Although it is probably not common practice to administer both plain and liposomal bupivacaine as we did in our study, an admixture of standard bupivacaine and liposomal bupivacaine was used as described by Gadsden's case report.[32] Concerns for a delayed onset with liposomal bupivacaine even with the admixture led the investigators to use general anesthesia with a laryngeal mask airway as part of the study protocol. Our results showed that intraoperative opioid consumption was not different between groups, which raises the question of whether the admixture can be used as a surgical anesthetic.

These findings are similar to what was found in three recent reviews and meta-analyses[28–30] on comparing perineural liposomal bupivacaine to standard bupivacaine. All three reviews found that perineural liposomal bupivacaine was associated with statistically but not clinically meaningful differences in pain scores compared with standard bupivacaine. This is consistent with what was found in recent reviews on surgeon-administered infiltration using liposomal bupivacaine.[19] Two reviews, Dinges *et al.*[28] and Ilfeld *et al.*,[29] used the same sole interscalene block study (Vandepitte[14]) for their analysis. Although these reviews included both infiltration and perineural application of liposomal bupivacaine in their analyses, a third review performed by Hussain et al.[30] investigated only perineural application of liposomal bupivacaine. This review used data from three interscalene studies: one published (Vandepitte) and two nonpublished studies that have data extracted from

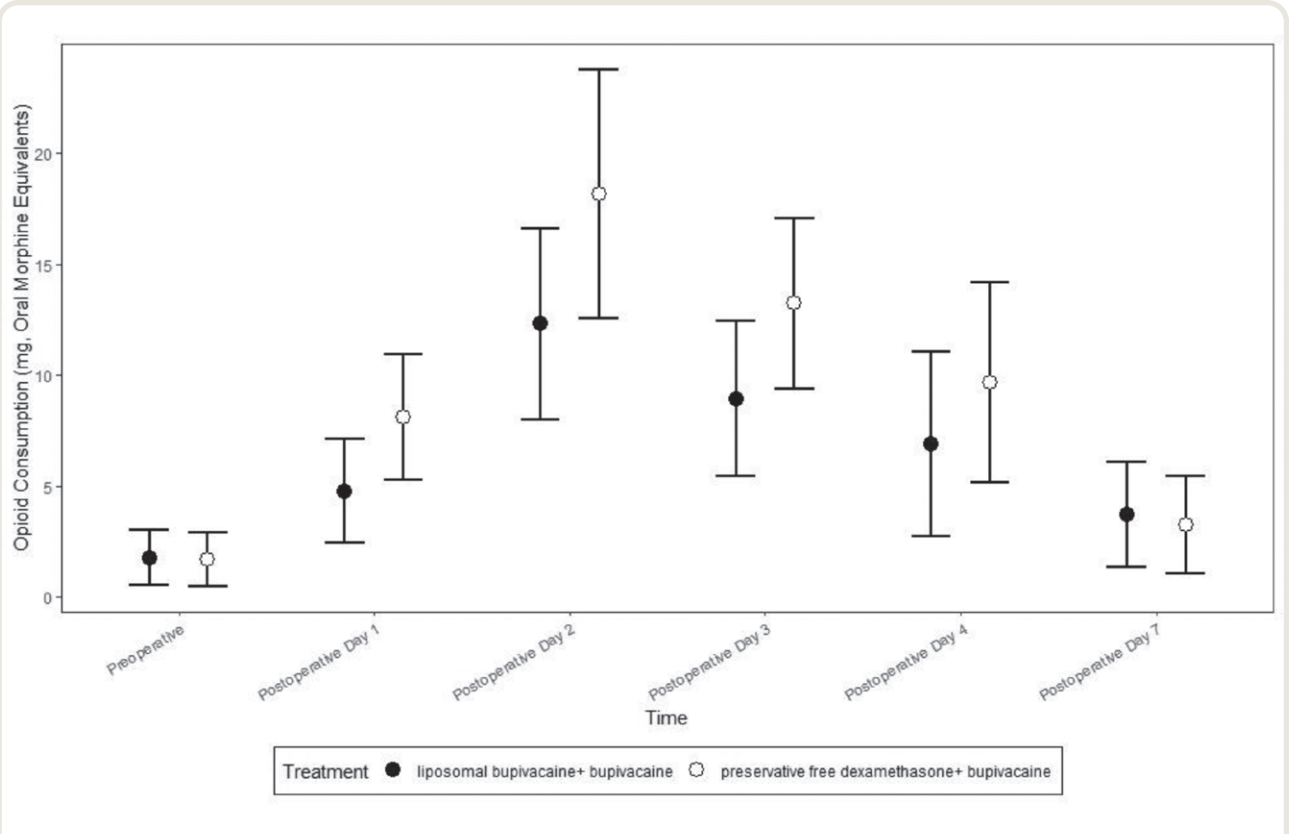

Fig. 3. Total opioid consumption over time. The data are plotted as means ± 95% CI for each randomization group over time.

clinicaltrials.gov. These studies bring to light the scarcity of published studies on liposomal interscalene nerve block.

Interscalene nerve blocks carry the inherent risk of phrenic nerve paresis.[33] Even when administering low volumes, such as 15 ml, the incidence was found to be 71%.[22] Prolonging the block raises the concern of risking hemidiaphragmatic paresis and possibly lengthening PACU or hospital stay, precluding its use in frail patients with pulmonary disease. Our study showed that both groups had similar rates of dyspnea (14% *vs.* 13%, $P = 0.907$) on postoperative day 1. Only one patient receiving liposomal bupivacaine was admitted for overnight observation. That patient was discharged the following day, less than 24 h after block administration. Another interscalene-related side effect, hoarseness, was found to be more common in the liposomal bupivacaine group (50% *vs.* 26%; $P = 0.014$) on postoperative day 1. There were no severe adverse effects and no neurologic complications in either group.

One additional aspect of our study deserves comment. This was a non–industry-sponsored study and was completely funded by the clinical revenue generated from our clinical practice (Department of Anesthesiology, Hospital for Special Surgery). Published data indicate that the presence of possible systematic bias favoring products that are made by the company funding the research.[34–36] A systematic review of 30 studies found that studies sponsored by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors (odds ratio = 4.05; 95% CI, 2.9 to 5.5).[34] An analysis of 182 randomized controlled trials found that industry-sponsored trials were more likely to have favorable results (superiority or noninferiority/equivalence for the experimental treatment) than non–industry-sponsored trials (odds ratio = 2.8; 95% CI, 1.6 to 4.7) with 96.5% (55 of 57) industry-funded noninferiority/equivalence trials obtaining a favorable result.[35] Finally, a Cochrane review noted that industry-sponsored studies more often had favorable efficacy results (relative risk = 1.3; 95% CI: 1.2, 1.4) and favorable conclusions (relative risk = 1.3; 95% CI: 1.2, 1.5).[36]

Our study has some limitations. First, because of the milky appearance of liposomal bupivacaine, the anesthesiologist performing the block could not be blinded to group allocation. This may influence anesthesiologist decision to be more readily willing to give intraoperative opioids. Second, the experience levels of staff administering the block varied. This could lead to a variability of accurate injection locations and volume given. With low-volume administration, it is possible that not all of the 15-ml admixture of 10 ml of 133 mg liposomal bupivacaine and 5 ml of 0.5% bupivacaine was administered in the proper location. However, we attempted to standardize the approach by

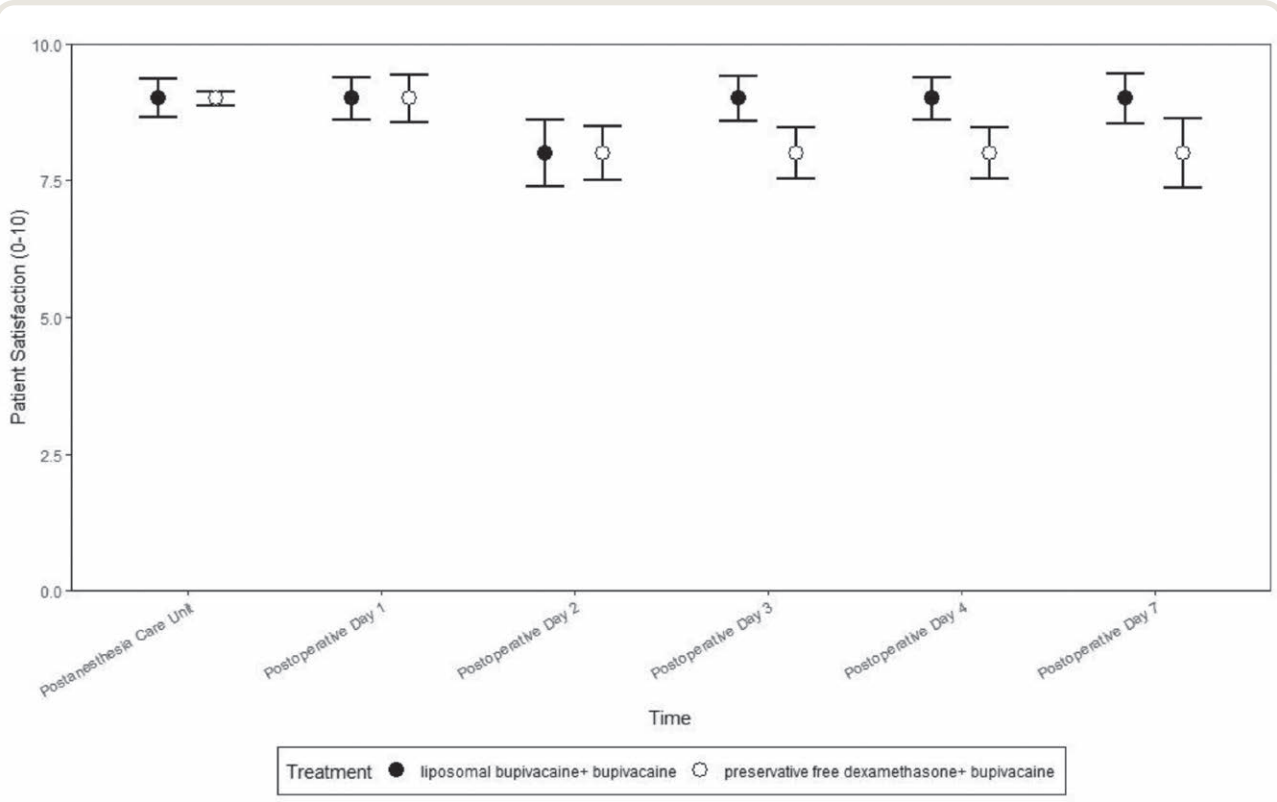

Fig. 4. Patient satisfaction over time. The data are plotted as means ± 95% CI for each randomization group over time.

agreeing to the technique before enrollment (in between C5 C6 nerve roots). Further, operators were randomly assigned, and thus both groups were equally exposed to varying levels of provider experience. Third, there might be recall bias because postdischarge information were collected *via* telephone interview. Fourth, our results may not be applicable to shoulder arthroplasty or might not be sufficient to be used as a primary surgical anesthetic. Further studies on dose–volume would need to be on liposomal bupivacaine to definitively determine the minimum amount needed to achieve surgical anesthesia. Last, while dexamethasone added into bupivacaine has been used clinically and reported in numerous studies, the clinicians are reminded that the use of dexamethasone in this manner remains as an off-label use.

In conclusion, perineural liposomal bupivacaine provided effective analgesia similar to that provided by perineural standard bupivacaine with dexamethasone. Given the large difference in cost, it seems prudent to reevaluate the role of liposomal bupivacaine in the setting of ambulatory shoulder surgery.

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Competing Interests

Dr. Memtsoudis is a director on the boards of the American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania) and the Society of Anesthesia and Sleep Medicine (Milwaukee, Wisconsin); a one-time consultant for Teikoku Pharma USA, Inc. (San Jose, California); a one-time consultant for Sandoz Inc. (Princeton, New Jersey); the holder of a U.S. Patent for the multicatheter infusion system (US-2017-0361063); the owner of SGM Consulting, LLC (Holmdel, New Jersey), and Centauros Healthcare Analytics and Consulting, LLC (Rumson, New Jersey); and a shareholder in Parvizi Surgical Innovations, LLC (Philadelphia, Pennsylvania), and HATH (Bedford Hills, New York). None of the above relations influenced the conduct of the current project. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: kimd@hss.edu. Raw data available at: kimd@hss.edu.

Correspondence

Address correspondence to Dr. Kim: 535 East 70th Street, New York, New York 10021. kimd@hss.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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