ANESTHESIOLOGY

Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia

A Systematic Review and Meta-analysis

Nasir Hussain, M.D., M.Sc., Richard Brull, M.D., Brendan Sheehy, M.D., Michael K. Essandoh, M.D., David L. Stahl, M.D., Tristan E. Weaver, M.D., Faraj W. Abdallah, M.D., M.Sc.

ANESTHESIOLOGY 2021; 134:147–64

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Liposomal bupivacaine was developed in an effort to extend the duration of local analgesia
- Despite the availability of many studies, it remains unclear whether and when liposomal bupivacaine offers significant advantages over the standard formulation

What This Article Tells Us That Is New

- Nine trials were included in a meta-analysis examining the difference in 24- to 72-h rest pain severity scores for liposomal and nonliposomal bupivacaine
- The area under the curve pain scores for the 24- to 72-h period were statistically but probably not clinically significant
- Secondary outcome analysis likewise failed to uncover benefits for liposomal bupivacaine regarding analgesic consumption, length of stay, and functional recovery

ABSTRACT

Background: Liposomal bupivacaine is purported to extend analgesia of peripheral nerve blocks when administered perineurally. However, evidence of the clinical effectiveness of perineural liposomal bupivacaine is mixed. This meta-analysis seeks to evaluate the effectiveness of perineural liposomal bupivacaine in improving peripheral nerve block analgesia as compared with nonliposomal local anesthetics.

Methods: The authors identified randomized trials evaluating the effectiveness of peripheral nerve block analgesic that compared liposomal bupivacaine with nonliposomal local anesthetics. The primary outcome was the difference in area under the receiver operating characteristics curve (AUC) of the pooled 24- to 72-h rest pain severity scores. Secondary outcomes included postoperative analgesic consumption, time to first analgesic request, incidence of opioid-related side effects, patient satisfaction, length of hospital stay, liposomal bupivacaine side effects, and functional recovery. AUC pain scores were interpreted in light of a minimal clinically important difference of 2.0 cm · h.

Results: Nine trials (619 patients) were analyzed. When all trials were pooled, AUC pain scores ± SD at 24 to 72 h were 7.6 ± 4.9 cm · h and 6.6 ± 4.6 cm · h for nonliposomal and liposomal bupivacaine, respectively. As such, perineural liposomal bupivacaine provided a clinically unimportant benefit by improving the AUC (95% CI) of 24- to 72-h pain scores by 1.0 cm · h (0.5 to 1.6; $P = 0.003$) compared with nonliposomal bupivacaine. Excluding an industry-sponsored trial rendered the difference between the groups nonsignificant (0.7 cm · h [–0.1 to 1.5]; $P = 0.100$). Secondary outcome analysis did not uncover any additional benefits to liposomal bupivacaine in pain severity at individual timepoints up to 72 h, analgesic consumption, time to first analgesic request, opioid-related side effects, patient satisfaction, length of hospital stay, and functional recovery. No liposomal bupivacaine side effects were reported.

Conclusions: Perineural liposomal bupivacaine provided a statistically significant but clinically unimportant improvement in the AUC of postoperative pain scores compared with plain local anesthetic. Furthermore, this benefit was rendered nonsignificant after excluding an industry-sponsored trial, and liposomal bupivacaine was found to be not different from plain local anesthetics for postoperative pain and all other analgesic and functional outcomes. High-quality evidence does not support the use of perineural liposomal bupivacaine over nonliposomal bupivacaine for peripheral nerve blocks.

(ANESTHESIOLOGY 2021; 134:147–64)

Liposomal bupivacaine used for infiltration[1–18] and field blocks[19–25] is proposed to provide extended postoperative analgesia up to 72 h[26,27] after various surgical procedures. Recently, the U.S. Food and Drug Administration (Silver Spring, Maryland) approved liposomal bupivacaine for perineural use in interscalene block of the brachial plexus.[28] However, evidence of the clinical effectiveness of perineurally applied liposomal bupivacaine in extending

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Submitted for publication July 27, 2020. Accepted for publication November 19, 2020. From the Department of Anesthesiology, The Ohio State University, Wexner Medical Center, Columbus, Ohio (N.H., B.S., M.K.E., D.L.S., T.E.W.); Department of Anesthesiology and Pain Medicine, University of Toronto, Canada (R.B., F.W.A.); Women's College Research Institute, Toronto, Canada (R.B., F.W.A.); and the Department of Anesthesiology and Pain Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada (F.W.A.).

 Anesthesiology 2021; 134:147–64. DOI: 10.1097/ALN.0000000000003651

<zdoi;. DOI: 10.1097/ALN.0000000000003651>

the duration of postoperative analgesia of peripheral nerve blocks is not definitive.[29] Indeed, a recent Cochrane review[30] of seven trials could not confirm the claim that liposomal bupivacaine improved analgesic outcomes.

This systematic review and meta-analysis aims to evaluate the effectiveness of perineural liposomal bupivacaine in improving peripheral nerve block analgesia, in comparison with nonliposomal local anesthetics, across various surgical procedures. We designated the difference in postoperative pain severity over the 24- to 72-h interval as a primary outcome. We also assessed the potential benefits of liposomal bupivacaine on short-term analgesic outcomes, as well as long-term outcomes, such as persistent postsurgical pain, opioid dependence, and health-related quality of life. Industry-sponsored trials were *a priori* considered a potential source of bias to be identified in the literature search and subsequent analysis.

Materials and Methods

The authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines in preparation of this study.[31] We searched for randomized trials that compared the effect of perineural liposomal bupivacaine with nonliposomal local anesthetics on short-term analgesic outcomes and other long-term outcomes in patients having surgery with peripheral regional anesthesia techniques. The created study protocol was not registered with the International prospective register of systematic reviews (PROSPERO).

Eligibility Criteria

Randomized trials of adult patients (18 yr or older) undergoing any type of surgery with peripheral nerve blocks that compared perineural liposomal bupivacaine with nonliposomal local anesthetics were considered. All types of single-injection peripheral nerve blocks were considered, regardless of dose or volume of liposomal bupivacaine used. Only nonliposomal local anesthetic (*i.e.*, not combined with liposomal bupivacaine) was considered as a comparator. Studies involving perineural adjuvants other than epinephrine were excluded. Studies of field blocks (*i.e.*, transversus abdominal block) and infiltration techniques (*i.e.*, port site infiltration or local infiltration analgesia) were not included to preserve homogeneity between studies. Studies of healthy volunteers were not eligible. Abstracts were not considered unless the full-text studies were available, and any foreign language studies were translated using an online translator.

Literature Search

A systematic search strategy was created by an evidence-based medicine librarian (L.B.) for the U.S. National Library of Medicine (Bethesda, Maryland) database (MEDLINE), Cochrane Database of Systematic Reviews, and Excerpta Medica database from inception to May 1, 2020. The search strategy was based on an initial search generated for MEDLINE (appendix 1). The strategy contained key words related to liposomal bupivacaine, pain, analgesic consumption, and postoperative analgesia. The reference lists of potentially eligible citations were also manually searched to identify additional trials that fulfilled inclusion criteria. We also reviewed the U.S. clinical trials registry (http://www.clinicaltrials.gov) for in-progress or completed clinical trials that satisfied our inclusion criteria. Finally, conference proceedings for the American Society of Anesthesiologists (Schaumburg, Illinois) 2011 to 2020 and American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania) 2013 to 2020 were electronically searched for potentially eligible citations.

Selection of Included Studies

Two reviewers (N.H. and B.S.) independently screened the titles and abstracts yielded by the literature search. The full texts of potentially eligible citations were then retrieved and evaluated for inclusion by the same independent reviewers. Any disagreement between the two reviewers was discussed until a consensus was reached. If consensus could not be reached between the two independent reviewers, a third reviewer (F.A.) made the final decision.

Data Extraction

A data extraction form was created using a Microsoft Excel (USA) spreadsheet and piloted by an independent reviewer (N.H). Data extraction was subsequently carried out independently by two reviewers (N.H. and B.S.). Any discrepancies in data extraction were discussed until a consensus was reached. If consensus could not be reached between the two independent reviewers, a third reviewer (F.A.) made the final decision.

The data extraction form collected information regarding the following variables: year of publication; participant age; publication year; type of surgery; surgical anesthetic; type of regional anesthetic technique; dose and volume of nonliposomal local anesthetic used; dose of volume of liposomal bupivacaine used; adjuvant used in local anesthetic solution; preoperative, intraoperative, and postoperative analgesic regimens; rest and dynamic pain scores at all reported times; analgesic consumption at all reported times; time to first analgesic request (duration of analgesia); opioid-related side effects; satisfaction with pain relief; hospital length of stay; liposomal bupivacaine–related side effects; functional recovery; and long-term outcomes including incidence of persistent postsurgical pain, health-related quality of life, opioid dependence, and pain-related disability. The primary source of data was numerical data presented in tables and figures. Data reported in graphical form were extracted with the assistance of graph digitizing software (GraphClick, Arizona Software, USA).

Assessment of Methodologic Quality and Risk of Bias

The methodologic quality of included trials was evaluated independently by two reviewers (N.H. and B.S.) using the Cochrane Collaboration tool for risk of bias assessment.[32] We conservatively assigned an "unclear risk of bias" to blinding of

personnel and outcome assessors' domain for those studies in which the methods did not provide sufficient details.

In addition, the methodologic quality for each outcome pooled across trials was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation[33,34] guidelines. The strength of evidence was then rated as being of high quality (⊕⊕⊕⊕), moderate quality (⊕⊕⊕⊖), low quality (⊕⊕⊖⊖), or very low quality (⊕⊖⊖⊖) evidence.

All quality assessments were done in duplicate by two independent reviewers (N.H. and B.S.). Any discrepancies in quality assessment were discussed until a consensus was reached. If consensus could not be reached between the two independent reviewers, a third reviewer (F.A.) made the final decision.

Primary and Secondary Outcomes

Because liposomal bupivacaine is promoted to improve duration and quality of analgesia beyond the first 24 h,[26,27,35] we selected analgesic outcomes that emphasized the 24- to 72-h time interval to evaluate the comparative clinical effectiveness of liposomal bupivacaine and nonliposomal local anesthetic. To that end, the primary outcome of this meta-analysis was designated as the 24- to 72-h difference in the weighted mean area under the curve (AUC) rest pain scores between patients receiving perineural analgesia inclusive of liposomal bupivacaine *versus* nonliposomal local anesthetics.

The secondary analgesic outcomes examined included cumulative oral milligram morphine equivalent consumption on days one (0 to 24 h), two (25 to 48 h), and three (49 to 72 h) postoperatively; postoperative rest pain severity (visual analog scale) scores at 1, 6, 12, 24, 48, and 72 h postoperatively; time to first analgesic request (hours); opioid-related side effects (nausea and vomiting, sedation/respiratory depression, pruritus, hypotension, urinary retention, or constipation); patient satisfaction; and hospital length of stay (hours). We also evaluated incidence of liposomal bupivacaine adverse effects (*i.e.*, hypesthesia, pyrexia, pruritus)[36]; postoperative functional recovery; and long-term outcomes, including the risk of persistent postsurgical pain, health-related quality of life, opioid dependence, and pain-related disability.

Measurement of Outcome Data

All measures of postoperative pain severity that were expressed as units of a 10-unit scale were converted to an equivalent score on the 0- to 10-cm visual analog scale score (0, no pain; and 10, worst pain possible).[37,38] Similarly, all measures of patient satisfaction were also converted to a 0- to 10-cm score (0, least satisfied; and 10, most satisfied).[38] All opioid consumption data were converted to cumulative oral morphine equivalents for the specific time interval (*i.e.*, 0 to 24 h, 25 to 48 h, 49 to 72 h).[39] Time-to-event data were presented in hours.

Statistical Analysis

The mean ± SD were sought for all continuous outcomes. When these were not available, statistical conversions[40–43] were made using the presented data to approximate these values. Specifically, the median and interquartile range were used to approximate the mean and SD when its value was not provided.[40] In situations where a mean and 95% CI was provided, conversions were made to a mean and SD using the methods described by the Cochrane Collaboration.[41] The median was used to approximate the mean in situations where it was the only value provided. If no measure of variance was provided, the value of the SD was imputed as a last resort.[42] This was done by calculating the pooled SD from all other studies included in the same outcome analyzed.[42] Finally, when needed for statistical pooling, categorical/ordinal data were converted to continuous form with corresponding mean ± SD using the natural units of the most familiar instrument.[38] In all circumstances, authors were contacted for additional results data, if needed.

For AUC analysis, the weighted mean difference (95% CI) in AUC of acute rest pain between liposomal bupivacaine and plain local anesthetic over the first 24- to 72-h postoperative period was calculated using the weighted means of the pooled rest pain scores during the 24-, 48-, and 72-h timepoints. The weighted means were then used to calculate the AUC for a specific time interval (*i.e.*, 24 to 48 h and 48 to 72 h). The results of individual studies were weighted by their overall sample size. This analysis was only conducted if (1) data were available for all three timepoints and (2) data for a specific timepoint was available from three or more studies.

For evaluation of the effect of liposomal bupivacaine on postoperative functional recovery, we *a priori* planned to report (1) the mean difference if all studies used the same continuous scale, (2) the log (odds ratio) if trials reported continuous data *and* used different tools measuring the same theme to assess postoperative function, or (3) an odds ratio if all trials reported binary outcomes. If scenario 2 was applicable, the conversion to log (odds ratio) from a standardized mean difference was done using the formula log (odds ratio) = standardized mean difference (π / $\sqrt{3}$),[44,45] under the assumption that the mean scores for each group followed a logistic distribution and that variances were equal between the two groups.

Meta-analysis

For continuous outcomes, pooling was performed using the inverse variance method because we anticipated clinical heterogeneity between studies. For dichotomous outcomes, pooling was performed using the Mantel–Haenszel random-effects model.[46] For our primary outcome, a weighted mean difference with 95% CI was calculated, and a two-tailed P value of < 0.05 was designated as the threshold of statistical significance.

For the continuous secondary outcomes of this review, a mean difference with 99% CI was calculated. For the dichotomous secondary outcomes, an odds ratio with 99% CI was calculated. Finally, for postoperative functional recovery, reporting depended on the nature of data (as described above).

The 99% CI was used for all secondary outcomes to decrease the risk of type I error associated with multiple testing, and a two-tailed *P* value of < 0.01 was designated as the threshold of statistical significance. To that end, we also used a threshold for statistical significance adjusted by the Bonferroni–Holm correction for comparisons in the secondary outcome analysis.[47]

Statistical pooling was only performed for those outcomes that had data from three or more studies. A qualitative evaluation was performed for those outcomes with fewer than three studies.

Interpretation of Outcome Results

For rest pain scores during the 24- to 72-h time interval, the results were interpreted in light of the minimal clinically important difference in pain scores for acute postoperative pain. This has been defined to be a 1.0-cm change on a 0- to 10-cm scale at an individual timepoint across a variety of surgeries.[48] For an AUC encompassing three measurements (24, 48, and 72 h), a threshold equivalent to 2.0 cm · h is calculated using the trapezoid method[49] and a minimum clinically important difference of 1.0 cm[48] for each of the three measurements.

Although not rigorously established, for cumulative opioid consumption during the 0- to 72-h interval, we considered a 30-mg difference in oral morphine consumption[50] (or 10 mg intravenous morphine) to be clinically important.

Assessment of Heterogeneity

For the primary outcome of this review (*i.e.*, 24- to 72-h difference in the AUC of rest pain scores), *a priori* sensitivity analysis was carried out by sequential exclusion of data from trials (1) published in nonindexed journals, (2) available as abstracts only, (3) published only in only U.S. Clinical Trials Registry, (4) with high-risk of bias in one or more domains of the Cochrane risk of bias tool, (5) that used other long-acting local anesthetics (*i.e.*, levobupivacaine or ropivacaine), and (6) supported by or declared conflict of interest with industry, specifically companies involved in manufacturing liposomal bupivacaine.

The extent of statistical heterogeneity in our secondary outcomes was assessed by calculating a percentage of variation (I^2) statistic, with values greater than 50% indicating significant heterogeneity. For instances of significant heterogeneity, the Grades of Recommendation, Assessment, Development, and Evaluation quality of evidence for an outcome were downgraded.

Assessment of Publication Bias

The risk of publication bias was assessed using the Egger's regression test when data from at least three trials were available for an estimate of effect.[51]

Data Management

Forest and funnel plots were generated using Review Manager Software (RevMan version 5.2; Nordic Cochrane Center, Denmark; Cochrane Collaboration). Sensitivity analysis and tests for publication bias were performed using Comprehensive Meta-Analysis 3.0 (Engelwood, USA).

Results

The literature search identified a total of 439 unique citations, and an additional 31 were identified after searching the U.S. Clinical Trials Registry. Thus, a total of 470 citations underwent screening based on title and abstract alone. Of these, 418 were excluded for many reasons, including incorrect comparison (n = 298), incorrect study design (n = 95), and incomplete study data (n = 26). The remaining 52 citations had their full-text versions retrieved or protocols reviewed for additional eligibility. After full-text screening, a total of 43 citations were excluded because of incorrect comparator (n = 42)[1–25,52–68] or lack of available data (n = 1).[69] As a result, a total of nine randomized trials were included in this review,[70–78] of which four[73–76] were from the U.S. Clinical Trials Registry and five[70–72,77,78] were published as full text. The flow diagram for study inclusion can be viewed in figure 1. Of these trials, the authors of one study declared conflicts of interest related to industry sponsorship.[71]

Study Characteristics

The study characteristics and outcomes included in this review are presented in table 1. The nine trials[70–78] involved 619 patients, of whom 316 received peripheral nerve blocks using perineural liposomal bupivacaine, and 303 received blocks with nonliposomal local anesthetics. Rest pain scores from 24 to 72 h postoperatively were assessed by all nine trials.[70–78] Eight of the trials reported opioid consumption beyond 24 h.[70–77] Specific details regarding the measures of pain assessed by the included trials can be viewed in appendix 2. The risk of bias assessment for all included studies can be viewed in figure 2.

The types of surgeries performed included major shoulder surgery,[71] rotator cuff surgery,[73] arthroscopic shoulder surgery,[76] hip arthroscopy,[70] total knee arthroplasty,[74] video-assisted thoracoscopic surgery,[75] minimally invasive lung resection,[77] inflatable penile prosthesis placement,[78] and total mastectomy.[72] The details of the peripheral nerve blocks techniques used are summarized in table 2. The blocks included interscalene nerve block,[71,73,76] adductor canal block,[74] intercostal nerve block,[75,77] dorsal penile block,[78] fascia iliaca block,[70] and pectoralis myofascial plane block.[72] The volume and dose of perineural liposomal bupivacaine ranged from 10 to 40 ml and 88 to 266 mg, respectively; one trial did not specify the dose used.[77] All studies compared the use of perineural liposomal bupivacaine to plain long-acting local anesthetic bupivacaine[70–77] or ropivacaine[78]; three studies[70,71,73] had additional study arms that mixed liposomal bupivacaine with plain bupivacaine.

Primary Outcome

AUC of Rest Pain over 24 to 72 h. Across 24 to 72 h,[70–74,76–78] the mean difference (95% CI) in AUC of rest pain was found to be 1.0 cm · h (0.5 to 1.6; $P = 0.003$) in favor of

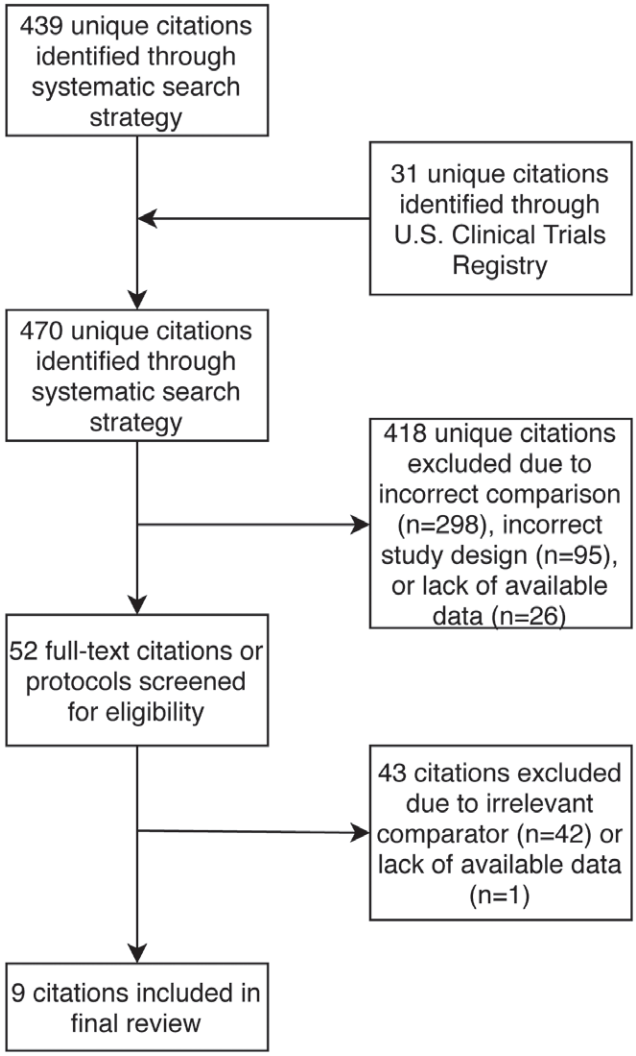

Fig. 1. Study flow diagram.

liposomal bupivacaine (fig. 3; appendix 3), but this difference failed to meet the threshold for clinical significance (*i.e.*, 2.0 cm · h; $P < 0.001$).

Importantly, the magnitude of treatment effect lost significance when the industry-sponsored trial[71] was excluded from analysis, with a mean difference of 0.7 cm · h (−0.1 to 1.5; $P = 0.100$). Heterogeneity also remained low ($I^2 < 50\%$) for all individual pain scores included in this analysis after exclusion of the industry-sponsored trial.[71] The remaining results were robust to sensitivity analysis after exclusion of (1) the study published in a nonindexed journal,[72] (2) those published only in the U.S. Clinical Trials Registry,[73,74,76] and (3) the single study[78] that used ropivacaine. Sensitivity analysis was not performed on studies available as abstracts and risk of bias assessment because no abstracts were included in the analysis and none of the included studies had a high risk of bias in multiple Cochrane risk of bias domains. Finally, the results were robust to *post hoc* sensitivity analysis by the sequential exclusion of trials[70,77] that required imputation to derive a mean ± SD. The quality of evidence was high and the risk of publication bias was low for all included timepoints.

Secondary Analgesic Outcomes

Rest Pain Severity at Individual Timepoints. Compared with nonliposomal bupivacaine, liposomal bupivacaine did not improve the mean difference (99% CI) of postoperative rest pain severity at 1 h (356 patients; liposomal bupivacaine, 172; nonliposomal bupivacaine, 184; mean difference, 0.4 cm [−0.2 to 0.9][70,72,74,77,78]); 24 h (521 patients; liposomal bupivacaine, 268; nonliposomal bupivacaine, 253; mean

Table 1. Study Characteristics and Outcomes of Interest Assessed in Included Studies

Groups (n)	N	Surgery	Surgical Anesthesia	Primary Outcome	Rest Pain Scores		Dynamic Pain Scores		Opioid Consumption		Time to First Analgesic Request	Opioid-related Adverse Effects	Liposomal Bupivacaine-related Adverse Effects	Patient Satisfaction	PACU Discharge Time	Hospital Discharge Time	Quality of Life Outcomes	Functional Outcomes	Persistent Pain	Author/ Year
					Early	Late	Early	Late	Early	Late										
1. Liposomal bupivacaine-interscalene nerve block (19) 2. Interscalene nerve block (20)	39	Rotator cuff repair	General anesthesia	Opioid consumption	•	•			•	•	•	•	•			•				Shariat 2013*
1. Liposomal bupivacaine-intercostal nerve block and liposomal bupivacaine-port site infiltration (49) 2. Intercostal nerve block and port site infiltration (49)	98	Video-assisted thoracoscopic surgery	General anesthesia	Opioid consumption		•				•			•			•	•		•	Khandhar 2015*
1. Liposomal bupivacaine-adductor canal block (31) 2. Adductor canal block (32)	63	Total knee arthroplasty	Spinal	Walking ability	•	•			•	•		•	•					•		Cios 2017*
1. Liposomal bupivacaine-interscalene nerve block (26) 2. Interscalene nerve block (24)	50	Rotator cuff repair or total shoulder replacement	General anesthesia	Pain scores	•	•			•	•			•	•				•		Vandepitte 2017
1. Liposomal bupivacaine-interscalene nerve block with dexamethasone (26) 2. Liposomal bupivacaine-interscalene nerve block (24) 3. Interscalene nerve block (26)	76	Rotator cuff repair	General anesthesia	Pain scores	•	•			•	•			•							Badman 2018*
1. Liposomal bupivacaine-dorsal penile nerve block (40) 2. Dorsal penile nerve block (47) 3. No block (44)	131	Inflatable penile prosthesis placement	General anesthesia	Pain scores	•	•			•											Xie 2018
1. Liposomal bupivacaine-fascia iliaca block (33) 2. Fascia iliaca block (37)	70	Hip arthroscopy	General anesthesia	Pain scores	•	•			•	•		•	•			•	•			Purcell 2019
1. Liposomal bupivacaine-pectoral myofascial plane block (43) 2. Pectoral myofascial plane block (43) 3. No block (43)	129	Total mammectomy	General anesthesia	Not specified	•	•				•	•	•				•				Zhang 2019
1. Liposomal bupivacaine-intercostal nerve block and liposomal bupivacaine-port site infiltration (25) 2. Intercostal nerve block and port site infiltration (25)	50	Robotic surgery or video-assisted thoracoscopic surgery	General anesthesia	Opioid consumption	•	•				•						•			•	Weksler 2020

Early: ≤ 24 h; late: > 24 h.

*Trial from http://www.clinicaltrials.gov.

PACU, postanesthesia care unit.

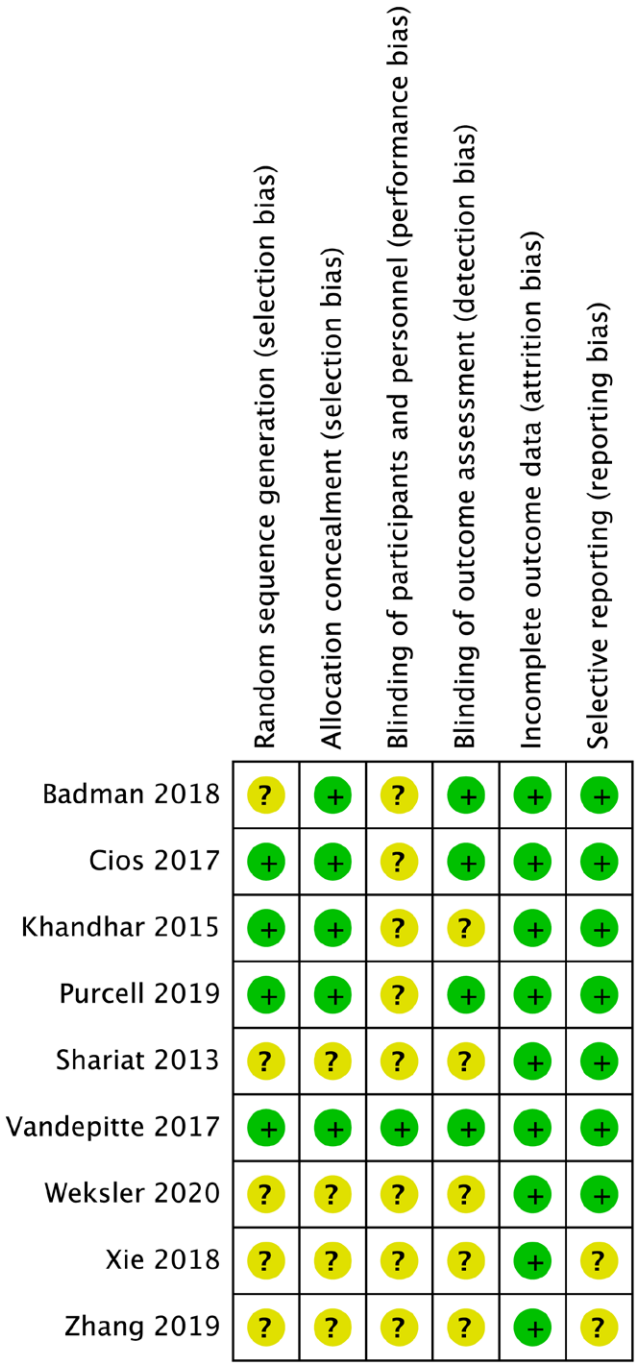

Fig. 2. Risk of bias assessment for included studies.

difference, 0.2 cm [−0.4 to 0.8][70–74,76–78]); 48 h (410 patients; liposomal bupivacaine, 215; nonliposomal bupivacaine, 195; mean difference, 0.5 cm [−0.2 to 1.2][70–74,76,77]); and 72 h (384 patients; liposomal bupivacaine, 203; nonliposomal bupivacaine, 182; mean difference, 0.3 cm [−0.3 to 0.8][70–74,76]; table 3). The quality of evidence was high for all timepoints, and the risk of publication bias was low.

Only one study[72] assessed postoperative rest pain severity at 6 and 12 h postoperatively. Qualitatively, no difference in rest pain severity at 6 and 12 h was observed between patients receiving liposomal bupivacaine and nonliposomal bupivacaine.

Opioid Consumption. For the 0- to 24-h interval, six studies[70,71,73,74,76,77] inclusive of 348 patients (liposomal bupivacaine,

Table 2. Local Anesthetic Techniques for Liposomal Bupivacaine and Analgesic Regiments of Included Studies

			Liposomal Bupivacaine Technique					
Preincisional Analgesia	Surgical Analgesia	Supplemental Postoperative Analgesia	Block Timing	Perineural Technique	Total Volume Injected	Dose	Mixed Plain Bupivacaine with Liposomal Bupivacaine	Author/ Year
Not specified	Not specified	Not specified	Preoperative	Interscalene nerve block	20 ml	88 mg	No	Shariat 2013*
None	IV fentanyl 1–2 μg/kg once; IV fentanyl as needed; IV ketorolac 30 mg once	Oral acetaminophen 1 g every 6 h for 5 d; IV ketorolac 15 mg every 6 h or oral ibuprofen 400 mg every 6 h; IV hydromorphone 0.5–1 mg every 2 h as needed or oral hydromorphone 2–4 mg every 4 h as needed	Intraoperative	Intercostal nerve block	Up to 20 ml	266 mg	No	Khandhar 2015*
IV fentanyl as needed	Spinal anesthesia	Oral toradol scheduled; oral acetaminophen scheduled; oral Celebrex 100–200 mg every 12 h; oral oxycodone as needed (therapy could vary)	Preoperative	Adductor canal block	20 ml	266 mg	No	Cios 2017*
Not specified	IV remifentanil 1–2 μg/kg per min; IV paracetamol 1 g once; IV ketorolac 0.5 mg/kg once	Oral paracetamol 1 g every 6 h; oral ibuprofen 400 mg every 8 h; oral tramadol 50 mg every 4 h as needed	Preoperative	Interscalene nerve block	15 ml	133 mg	Yes	Vandepitte 2017
Not specified	Not specified	Not specified	Preoperative	Interscalene nerve block	25 ml	133 mg	Yes	Badman 2018*
Not specified	Not specified	Oral acetaminophen-oxycodone as needed; IV morphine as needed	Intraoperative	Dorsal penile nerve block and penile ring block	20 ml	266 mg	No	Xie 2018
Oral acetaminophen 975 mg once; oral celecoxib 200 mg once; oral oxycodone 10 mg once; oral gabapentin 600 mg once	IV opioid as needed	Oral oxycodone extended release 10 mg every 12 h; oral celecoxib 200 mg daily for 2 wk; oral acetaminophen 975 mg as needed; oral oxycodone 5 mg as needed	Preoperative	Fascia iliaca block	40 ml	266 mg	Yes	Purcell 2019
IV sufentanil 10–15 μg once	IV sufentanil 0.3 μg/kg once; IV remifentanil infusion	Not specified	Preoperative	Pectoralis myofascial plane block	30 ml	266 mg	No	Zhang 2019
Not specified	Not specified	IV ketorolac 15 mg every 6 h for 2 d as needed; oral oxycodone 5 mg every 6 h (once chest tube removed); oral acetaminophen 325 mg every 6 h (once chest tube removed); PCA morphine or hydromorphone	Intraoperative	Intercostal nerve block	10 ml	Not specified	No	Weksler 2020

*Trial from www.clinicaltrials.gov.
IV, intravenous; PCA, patient-controlled analgesia.

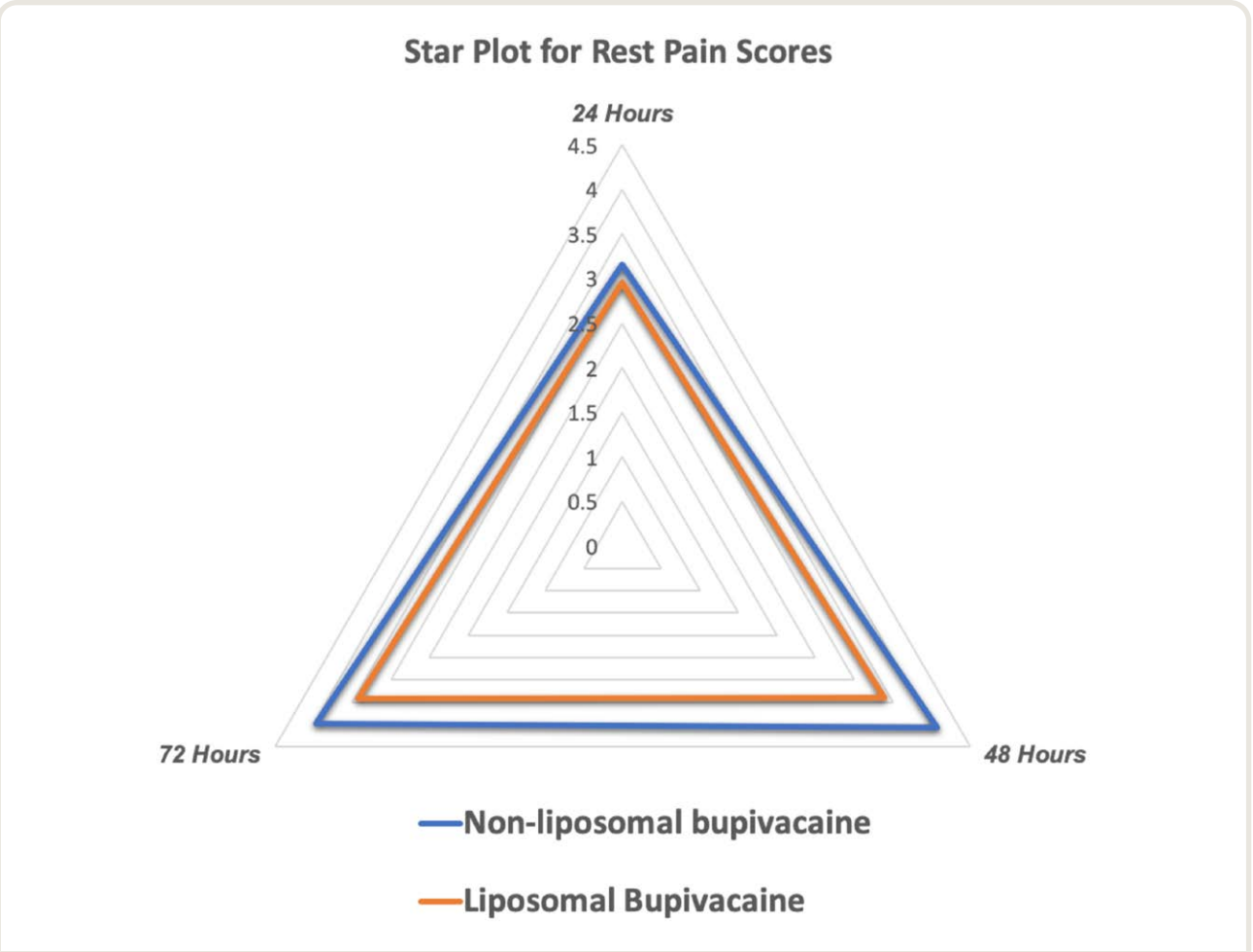

Fig. 3. Graphical representation of the area under the curve of the pooled weighted mean pain scores at rest as measured by the visual analog scale (0 to 10 cm) over time for liposomal bupivacaine *versus* nonliposomal bupivacaine.

185; nonliposomal bupivacaine, 163) reported analgesic consumption. Liposomal bupivacaine was not different than nonliposomal bupivacaine for this outcome, with a mean difference (99% CI) of 1 mg (−3 to 6; table 3). The quality of evidence was high and the risk of publication bias was low.

For the 25- to 48-h interval, six studies[70,71,73,74,76,77] inclusive of 348 patients (liposomal bupivacaine, 172; nonliposomal bupivacaine, 152) reported analgesic consumption. Liposomal bupivacaine was not different than nonliposomal bupivacaine for this outcome, with a mean difference (99% CI) of 7 mg (−3 to 16; table 3; fig. 4). The quality of evidence was moderate owing to heterogeneity in the pooled estimate and the risk of publication bias was low.

For the 49- to 72-h interval, six studies[70–74,76] inclusive of 298 patients (liposomal bupivacaine, 160; nonliposomal bupivacaine, 138) reported analgesic consumption. Liposomal bupivacaine was not different than nonliposomal bupivacaine for this outcome, with a mean difference (99% CI) of 4 mg (−2 to 10; table 3). The quality of evidence was high and the risk of publication bias was low.

Time to First Analgesic Request. Three studies[71,72,76] inclusive of 175 patients (liposomal bupivacaine, 89; nonliposomal bupivacaine, 86) reported time to analgesic request. Liposomal bupivacaine was not different than nonliposomal bupivacaine for this outcome, with a mean difference (99% CI) of −1.3 h (−5.3 to 2.7; table 3). The quality of evidence was high and the risk of publication bias was low.

Opioid-related Side Effects. Three studies[72,74,76] inclusive of 188 patients (liposomal bupivacaine, 94; nonliposomal bupivacaine, 94) reported opioid-related side effects. At 72 h, 17 of 94 patients and 23 of 94 patients experienced nausea/vomiting in the liposomal bupivacaine and nonliposomal bupivacaine groups, respectively; no statistical difference was observed between the two groups. The quality of evidence was high and the risk of publication bias was low.

Patient Satisfaction. Only one study[71] reported satisfaction with pain relief. Qualitatively, patients receiving liposomal bupivacaine were more satisfied than those receiving and nonliposomal bupivacaine.

Table 3. Primary Secondary Endpoint Results

Outcome	Studies included	Nonliposomal Bupivacaine, Mean ± SD or n/N	Liposomal Bupivacaine, Mean ± SD or n/N	Mean Difference or Odds Ratio (99% CI)	*P* Value for Statistical Significance	Bonferroni–Holm Threshold for Statistical Significance	*P* Value for Heterogeneity	I^2 Test for Heterogeneity	Quality of Evidence (Grades of Recommendation, Assessment, Development, and Evaluation)
Primary outcome									
AUC pain scores over 24–72 h	8	7.6 ± 4.9	6.6 ± 4.6	1.0 (0.5 to 1.6)*	0.003	Not applicable	Not applicable	Not applicable	⊕⊕⊕⊕
Secondary outcomes									
Rest pain at 1 h (cm)	5	3.2 ± 2.8	2.8 ± 2.8	0.4 (–0.2 to 0.9)	0.117	0.001	0.181	36%	⊕⊕⊕⊕
Rest pain at 24 h (cm)	8	3.2 ± 2.4	3.0 ± 2.5	0.2 (–0.4 to 0.8)	0.334	0.002	0.114	40%	⊕⊕⊕⊕
Rest pain at 48 h (cm)	7	4.1 ± 2.5	3.4 ± 2.3	0.5 (–0.2 to 1.2)	0.060	0.001	0.117	42%	⊕⊕⊕⊕
Rest pain at 72 h (cm)	6	4.0 ± 2.5	3.4 ± 2.1	0.3 (–0.3 to 0.8)	0.234	0.002	0.204	32%	⊕⊕⊕⊕
Oral morphine consumption at 0–24 h (mg)	6	27 ± 30	22 ± 23	1 (–3 to 6)	0.428	0.005	0.200	29%	⊕⊕⊕⊕
Oral morphine consumption at 25–48 h (mg)	6	29 ± 30	21 ± 23	7 (–3 to 16)	0.062	0.001	0.008	68%	⊕⊕⊕⊖
Oral morphine consumption at 49–72 h (mg)	5	21 ± 22	15 ± 20	4 (–2 to 10)	0.077	0.001	0.062	49%	⊕⊕⊕⊕
Time to analgesic request (h)	3	17.7 ± 28.1	19.4 ± 28.3	–1.3 (–5.3 to 2.7)	0.391	0.003	0.335	13%	⊕⊕⊕⊕
Opioid-related side effects	3	23/94	17/94	1.5 (0.6 to 3.9)	0.267	0.002	0.823	0%	⊕⊕⊕⊕
Length of hospital stay (d)	4	3.6 ± 4.7	3.9 ± 4.9	–0.1 (–0.3 to 0.2)	0.522	0.010	0.189	37%	⊕⊕⊕⊕
Liposomal bupivacaine-related adverse effects	6	Not applicable	0/208	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Rest pain at 6 and 12 h, patient satisfaction, functional recovery, persistent postsurgical pain, opioid dependence, and health-related quality of life outcomes are not shown because the outcome reported by fewer than two studies or was not measured.
⊕⊕⊕⊕, high-quality evidence; ⊕⊕⊕⊖, moderate quality evidence; ⊕⊕⊖⊖, low-quality evidence, ⊕⊖⊖⊖, very low-quality evidence.

*Primary outcome with 95% CI shown.

AUC, area under the curve.

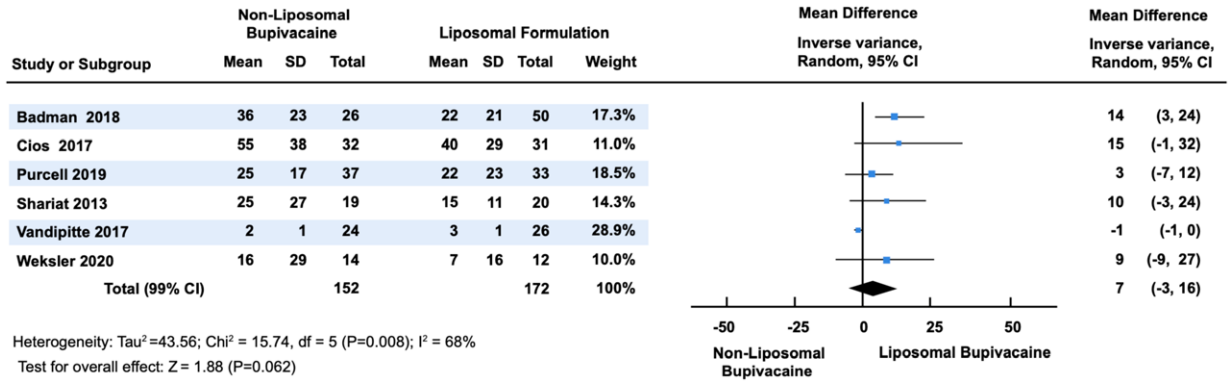

Fig. 4. Forest plot of cumulative oral morphine equivalent consumption at 25 to 48 h for liposomal bupivacaine *versus* nonliposomal bupivacaine. Pooled estimates of the weighted mean difference are shown with 99% CI. Pooled estimates are represented as *diamonds*, and *lines* represent the 99% CI.

Length of Hospital Stay. Four studies[70,72,75,77] inclusive of 304 patients (liposomal bupivacaine, 150; nonliposomal bupivacaine, 154) reported time to analgesic request. Liposomal bupivacaine was not different than nonliposomal bupivacaine for this outcome, with a mean difference (99% CI) of −0.1 days (−0.3 to 0.2; table 3). The quality of evidence was high and the risk of publication bias was low.

Liposomal Bupivacaine-related Adverse Effects

Six studies,[70,71,73–76] inclusive of 209 patients who received liposomal bupivacaine, assessed medication-related side effects (*i.e.*, hypesthesia, pyrexia, pruritus). Overall, no side effects were reported in any of these studies.

Functional Recovery

Two studies[71,74] reported postoperative function at 24 h. One study measured quadriceps strength,[74] and another assessed hand grip strength.[71] Qualitatively, no difference was observed between patients receiving liposomal bupivacaine and nonliposomal bupivacaine.

Long-term Outcomes

One study[75] assessed persistent pain at 30 days after surgery, and another[77] assessed this outcome at 90-day follow-up. Qualitatively, no difference was observed between patients receiving liposomal bupivacaine and nonliposomal bupivacaine. Opioid dependence and health-related quality of life were not assessed in any of the trials.

Discussion

Our systematic review and meta-analysis provides high-quality evidence demonstrating that using liposomal bupivacaine perineurally in peripheral nerve blocks provides a statistically significant but clinically unimportant improvement in the AUC of postoperative pain scores compared with nonliposomal bupivacaine. Furthermore, exclusion of an industry-sponsored trial rendered this benefit insignificant. Level I evidence indicates that the liposomal formulation examined in this review is not different from nonliposomal bupivacaine for the analgesic outcomes examined, including acute rest pain severity and analgesic consumption up to 72 h postoperatively. This lack of difference was consistent across all outcomes and for all timepoints measured, up to 3 days postsurgery. These findings undermine the rationale for using liposomal bupivacaine perineurally and the justification for the associated extra costs.[27,79,80] Practitioners seeking prolonged analgesia should consider other proven modalities, including catheter-based continuous blocks and local anesthetic adjuncts.[81–85]

Structurally, the liposomal local anesthetic preparation examined in this review features encapsulation by a multivesicular liposomal lipid bilayer, allowing sustained local anesthetic release, theoretically prolonging its effect up to 72 h after a single application.[86–88] Pharmacokinetic studies seem to corroborate this slow release, showing sustained plasma bupivacaine levels up to 96 h[86,87] and even 120 h after interscalene brachial plexus block.[87] However, our review of clinical evidence of effectiveness of the perineural route in prolonging the duration of peripheral nerve block analgesia has demonstrated disparity with the anticipated benefits. Although this is a novel finding for the perineural route, it may not be totally new for liposomal bupivacaine. Several recent systematic reviews[27,30,89–97] and an editorial[29] examining the evidence for surgeon-administered local infiltration analgesia using liposomal bupivacaine have questioned its effectiveness. Curiously, the underlying causes of both perineural and infiltration routes failing to provide incremental benefits when compared with nonliposomal bupivacaine,[98,99] and even placebo (normal saline),[12] may be similar. One plausible explanation is that pH disparity makes liposomal bupivacaine stagnate extracellularly in the tissue in which it was injected, leading to failures in penetrating cells,

interrupting signal transmission, and providing analgesia. As bupivacaine makes its initial contact with the tissue in which it is injected, it triggers a localized inflammatory response[100] that renders the medium acidotic,[101] impeding further tissue penetration by the subsequent bupivacaine molecules that are slowly released from the lipid-based depots (DepoFoam; Pacira Pharmaceuticals, USA).[102] Thus, local anesthetic-induced inflammatory changes may be the main reason that liposomal bupivacaine was unable to surpass the clinical effectiveness of nonliposomal bupivacaine.

Our review comes with several strengths. First, our systemic search strategy was exhaustive and captured both published and ongoing studies from the U.S. Clinical Trials Registry. Second, all estimates of effect were of high quality and characterized by low levels of heterogeneity, strengthening the internal validity of this review. Third, although a Cochrane review has addressed this topic in 2017,[30] we were able to provide readers with additional results for outcomes that have not been previously investigated because of a lack of data, such as AUC of pain analysis and analgesic consumption at 48 and 72 h postoperatively. Fourth, we presented 99% CI for all secondary outcomes to reduce the risk of type I error and multiple testing bias. Finally, the sensitivity analysis, by excluding the industry-sponsored trial, seems to have successfully eliminated bias, as the excluded data influenced the initial analysis toward a robust benefit favoring perineural liposomal bupivacaine.

Our review also comes with notable limitations. First, we investigated perineural liposomal bupivacaine across a variety of surgical procedures and block techniques. This could potentially limit the external validity of our results and limit their broad applicability; nonetheless, the low level of statistical heterogeneity disputes this possibility. Second, the choice of AUC for pain severity scores as a primary outcome limited our ability to perform additional ancillary analyses, such as meta-regression, to investigate the impact of potentially relevant covariates on the estimate of effect. In addition, AUC analysis may be more prone to bias given that a significant difference is more likely to be detected than in individual timepoint analysis. Nonetheless, analysis of individual timepoints was confirmatory of the findings. Third, variabilities in the analgesic regimens used in the included studies may have played a confounding effect. Fourth, we cannot exclude the possibility of publication bias, because we did not include unpublished negative trials or missing studies. Finally, owing to scarcity of data, we were unable to statistically evaluate clinically important long-term outcomes such as pain-related disability, persistent pain, opioid-dependence, and health-related quality of life.

Conclusions

Used perineurally in peripheral nerve blocks, liposomal bupivacaine provides a clinically unimportant improvement in the AUC of postoperative pain scores compared with nonliposomal bupivacaine. Furthermore, excluding an industry-sponsored trial rendered this benefit insignificant. We also found liposomal bupivacaine to be not different from nonliposomal bupivacaine for all other analgesic and functional outcomes. High-quality evidence does not support the use of perineural liposomal bupivacaine over nonliposomal bupivacaine for peripheral nerve blocks.

Acknowledgments

The authors thank Laura Banfield, M.L.S., Ph.D. (Health Sciences Library, McMaster University, Hamilton, Ontario, Canada), for creating the search strategy for this meta-analysis.

Research Support

Support for this study was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Essandoh is a consultant for Boston Scientific (Marlborough, Massachusetts) and S4 Medical (Cleveland, Ohio). Dr. Weaver is a consultant for Medtronic (Dublin, Ireland). The remaining authors declare no competing interests.

Correspondence

Address correspondence to Dr. Abdallah: Department of Anesthesiology and Pain Medicine, University of Toronto, North York General Hospital, 4001 Leslie St., Toronto, ON M2K 1E1, Canada. FAbdallah@mail.utoronto.ca.

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Appendix 1. Search Strategy Based on Initial MEDLINE Search

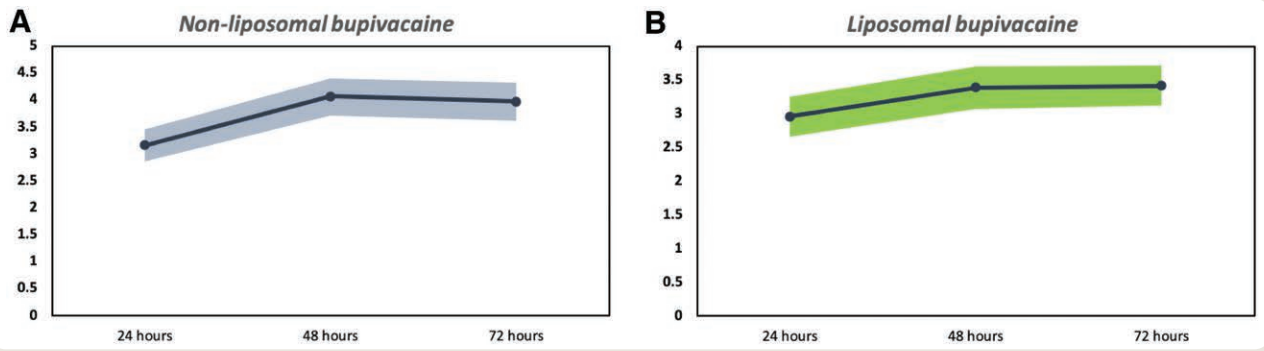
1 exparel.mp. (101)
2 ((liposom* or depo*) adj5 bupiv?caine).mp. (608)
3 1 or 2 (615)
4 su.fs. (1998623)
5 ((post-operat* or postoperat* or post-surg* or post or analg* or surg*) adj5 pain*).mp. (93771)
6 ((post-operat* or postoperat* or post-surg* or post or surg*) adj5 analg*).mp. (20124)
7 4 or 5 or 6 (2060618)
8 7 and 3 (439)
9 remove duplicates from 8 (438)

Appendix 2. Elements of Outcomes Assessed for Rest Pain Scores

Author, Year	Domain	Specific Measurement	Specific Metric	Method of Aggregation	Timepoint
Shariat 2013	Rest pain	Numeric Rating Scale (0–10)	Value at a timepoint	Mean	Postoperative days 1, 2, 3, and 7
Khandhar 2015*	Rest pain	Visual Analog Scale (0–10)	Value at a timepoint	Median	Postoperative day 7
Cios 2017	Rest pain	Visual Analog Scale (1–10)	Value at a timepoint	Mean	Postoperative days 0, 1, 2, and 3
Vandepitte 2017	Rest pain	Numeric Rating Scale (0–10)	Value at a timepoint	Mean	Presurgery; postoperative days 1, 2, 3, 4, and 7
Badman 2018	Rest pain	Visual Analog Scale (0–10)	Value at a timepoint	Mean	Postoperative days 1, 2, 3, and 4
Xia 2018	Rest pain	Visual Analog Scale (0–10)	Value at a timepoint	Mean	Postoperative days 1, 2, 3, 4, 5, 6, 7, and 8
Purcell 2019*	Rest pain	Defense and Veterans Pain Rating Scale (0–10)	Value at a timepoint	Median	Postanesthesia care unit; postoperative days 1, 2, 3, and 14
Zhang 2019	Rest pain	Numeric Rating Scale (0–10)	Value at a timepoint	Mean	Postanesthesia care unit; postoperative 4 h and 12 h; postoperative days 1, 2, and 3
Weksler 2020*	Rest pain	Visual Analog Scale (0–10)	Value at a timepoint	Median	Postoperative days 0, 1, 2, 14, and 90

*Imputation performed to derive mean and SD.

Appendix 3. Band Plot for Rest Pain Scores with 95% CI across 24, 48, and 72 h for Nonliposomal Local Anesthetic and Liposomal Bupivacaine



	Nonliposomal Bupivacaine		Liposomal Bupivacaine	
Timepoint	Sample size	Mean Visual Analog Pain Scale Score (95% CI)	Sample size	Mean Visual Analog Pain Scale Score (95% CI)
24 h	268	3.2 (2.9–3.5)	253	3.0 (2.7–3.3)
48 h	195	4.1 (3.7–4.4)	215	3.4 (3.1–3.7)
72 h	181	4.0 (3.6–4.3)	203	3.4 (3.1–3.7)

Also presented are estimates of effect included in each figure.