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Research Article

Intraoperative Liposomal Bupivacaine Does Not Reduce Opioid Use vs. Ropivacaine: A Systematic Review

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Abstract

Introduction: Liposomal bupivacaine (LB) is a long-acting analgesic that, due to its liposomal formulation, purportedly extends its analgesic effect up to 72 hours. However, the clinical efficacy of LB appears mixed. This systematic review seeks to evaluate the effectiveness of liposomal bupivacaine in improving postoperative outcomes compared to ropivacaine (ROPI), another commonly used long-acting analgesic.

Materials and Methods: Prospective and randomized controlled trials (RCTs) evaluating the efficacy of LB compared to ROPI were selected for review. Primary outcomes included hospital length of stay (LOS) and postoperative opioid consumption measured in oral morphine equivalents (OME). Secondary outcomes included analgesic cost.

Results: 14 studies met the review criteria. We found that LB and ROPI are equivalent in managing postoperative pain. 8 of the 14 trials reported equal efficacy between LB and ROPI as determined by OME post-procedure and 10 of the 14 trials reported similar LOS after surgery. These findings remained consistent across multiple surgical procedures and multiple drug administrative modalities.

Conclusion: Our systematic review found that LB was not superior to ROPI in reducing postoperative OME use and hospital LOS. The only consistent finding was the significantly increased cost of LB compared to that of ROPI. Therefore, the use of LB over ROPI cannot be justified.

Keywords: Exparel; Liposomal Bupivacaine; Pain Management; Postoperative Hospital Length of Stay; Postoperative Oral Morphine Equivalent; Ropivacaine

Introduction

Adequate treatment of postoperative pain is a significant issue in clinical settings, and often leads to the use and potential overuse of opioid medication. The use of opioids as a mainstay of pain management has resulted in numerous sociological, economic, and bioethical problems, most pertinently a nationwide opioid addiction epidemic that the HHS declared a public health emergency in 2017. [1] From 1999 to 2019, nearly 500,000 people have died of opioid related overdoses in the United States per the CDC report on Drug Overdose. [2] This loss of life underscores the clinical importance of careful peri- and postoperative pain management to optimize patient outcomes beyond their immediate hospital stay. Multi-modal pain management has become one of the mainstay avenues to address this issue. Long-acting local anesthetics have emerged

as an area of interest, offering a potential solution as an alternative pain management modality to mitigate postoperative use of opioid analgesics. [3] These long-acting anesthetics first emerged as part of clinical practice in 1943 with the introduction of lidocaine, administered preoperatively with an analgesic effect lasting 30 minutes to 3 hours. [4] Ropivacaine (ROPI) and plain bupivacaine (BUPI) then followed, providing pain relief for 3-6 hours and 4-9 hours respectively. Their mechanism of action is via direct GPCR receptor inhibition which includes NK-1 receptors for Substance P, a neuromodulator specific to pain. [5] By blocking Substance P, local analgesics can provide a long-acting neuromodulation of pain for patients undergoing surgical procedures at the site of their wounds.

The most recent addition to long-acting analgesics is liposomal bupivacaine (LB), which was approved by the FDA in 2011 for prolonged pain control for up to 72 hours per dose. [6] LB is composed of plain BUPI and DepoFoam multivesicular liposomes encapsulating the BUPI. The multivesicular liposomes act as an extended release drug delivery technology, allowing for slow release of the active BUPI as the liposomes degrade. [7] LB was approved following two phase III randomized control trials (RCT) for hemorrhoidectomy and bunionectomy. [8,9] The methods of administration approved by the FDA are transversus abdominis plane blocks, interscalene nerve blocks for shoulder surgery, and local surgical site infiltration, such as for mammoplasty, total knee arthroplasty (TKA), and inguinal hernia repair. LB has also been used for off-label and for investigational use as peripheral nerve blocks, intra-articular use for TKAs, epidural use, and intercostal nerve blocks. [3] When the FDA approves a drug for clinical use, studies need only compare the relative outcomes of the drug in question to those of a placebo, as was the case for the phase III clinical trials that resulted in LB coming to market. [10] In addition, pain is intrinsically hard to quantify, as much of the data is based on self-reported pain scores which are inherently subjective and thus prone to bias. Physicians are then tasked with determining through clinical investigations, post FDA approval, whether LB is more effective than alternatives on the market. For the reasons articulated above, the relative efficacy of LB compared to its competitors remained undetermined when hospitals began acquiring the product at a significant price premium compared to ROPI or plain BUPI.

LB manufacturer, Exparel, publicly lists their pricing as $198.84 per 133 mg dose and $354.53 per 266 mg dose. [11] ROPI and plain BUPI are sold by multiple pharmaceutical companies and as such the prices vary. As a representative example, wholesale medical supplies distributor McGuff Medical Products currently sells 0.5% ROPI in 30 ml vials for $13.55 per vial and BUPI 0.5% in a 50 ml vial for $5.53 per vial. [12,13] The difference in price should prompt health providers to investigate the efficacy of LB. Without conclusive evidence that LB is better than its competitors in any meaningfully way, hospitals risk needlessly increasing expenses without improving patient outcomes. If patient pain relief is substantial enough to shorten postoperative hospital stay, it is possible that there is a dual benefit to LB use: curbing both hospital costs and minimizing opioid use in the immediate postoperative period, potentially lowering subsequent dependency. It is this potential that forms the impetus for our systematic review.

Since 2011, the literature reviewing differences between LB and plain BUPI has found mixed results regarding the efficacy of LB. [14,15] As LB is plain BUPI engineered with liposomal technology, it makes sense that the first wave of literature compared studies using both ingredients. However, there is less material focusing on LB vs ROPI. ROPI is the second longest long-acting local analgesic agent after LB, and it is of clinical importance to know which one is more effective in the immediate postoperative period. Our study, then, is to compare outcomes after intraoperative LB and ROPI use with regards to postprocedural opioid usage as well as hospital length of stay. This review will analyze if the benefits of LB justify the price, i.e. whether increased reliance on LB can result in reduced hospitals costs through shortened stays, and/or whether LB might contribute to curbing the use of opioids by reducing the use of addictive medications for postoperative pain management. We hypothesize that the change in postprocedural opioid usage and hospital length of stay for LB compared to ROPI will not justify the vastly increased price of LB.

Methods

A literature review was performed using Embase (Elsevier), PubMed, the Cochrane Library, and MEDLINE (Ovid) from inception until June 10th, 2022. The search terms were selected using MEDLINE Medical Subject Heading terms (MeSH) “ropivacaine” AND “bupivacaine” OR “liposomes” AND “anesthetics, local” AND “extended release” as well as any synonyms suggested by PubMed entry terms. The same terms were input into Embase and MEDLINE using their respective database syntax, and any articles not already found in PubMed were added for review. Each of these articles were then reviewed by two researchers. An a priori inclusion/exclusion checklist was used to assess whether articles should be included in the analysis. Each researcher reviewed the list independently and then compared inclusion decisions together. A faculty advisor was available as a third reviewer in case of arbitration.

The inclusion criteria are based on the PICOT model: [16] 1) the study needed to compare outcomes related to a surgical procedure; 2) one arm of the study used LB; 3) another arm used ROPI; and 4) the studies report outcomes concerning opioids administered to participants measured in oral morphine equivalents (OME) in the postoperative period and/or hospital length of stay

(LOS). The results were then organized based on primary outcomes: OME and LOS. Along with the primary outcomes, LOS and OME, information on avenue of analgesia administration as well as drug costs was collected for reporting and analysis, if available. Only RCTs and prospective studies were included in this review. Published preclinical material, retrospective cohort articles, textbook chapters, and opinion pieces (Letters to the Editor), and case studies were not included. While review articles were not included, they were consulted, and any relevant trials cited were also included in the review. Studies were excluded if they did not report outcomes with analysis, for example if the outcomes were only included as descriptive statistics or a component of a chart where significance was not included (Figure 1).

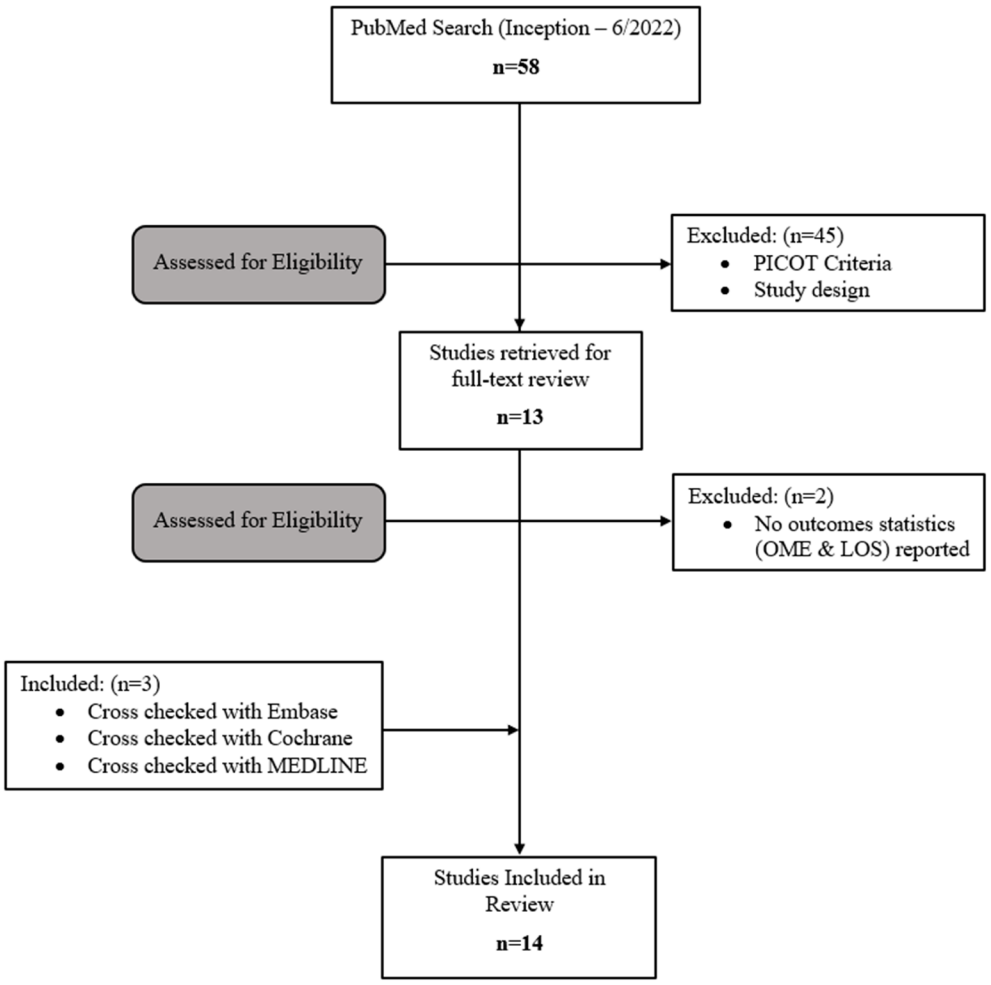

Figure 1: Study selection diagram detailing inclusion and exclusion.

Eligible articles were then assessed using The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria. GRADE has four levels of evidence to quantify the certainty in evidence or quality of evidence of each study: very low, low, moderate, and high. Evidence from randomized controlled trials starts at high quality while observational data starts at low quality. Additional GRADE domains rating calculations that can adjust the score down include: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, and 5) publication bias to assess the overall quality of evidence. [17-21] The quality of evidence for each study is then applied to each study outcome independently, as this often varies. [22,23] Through the GRADE criteria, the included studies were rigorously and systematically evaluated the to determine their strength. The results were then analyzed as a whole, based on the GRADE criteria to assess the certainty of the overall findings.

Results

58 articles on PubMed met the literature review criteria. 45 articles were excluded as they were not RCTs or they did not directly compare ROPI vs LB in the setting of a surgical procedure. An additional 2 studies were also excluded because of failure to report outcomes pertaining to postoperative OME or LOS. The remaining 11 articles were then cross-checked with three other databases: Embase, MEDLINE and Cochrane. Through this search, three additional articles were found to meet inclusion criteria and added to the study. Ultimately, 14 studies were included in the literature review and their findings pertaining to OME and LOS can be viewed in Table 1. All included studies were trials of orthopedic procedures. The studies addressed the following surgical procedures: 7 Total Knee Arthroplasties (TKA), 5 Total Shoulder Arthroplasties (TSA), 1 Total Hip Arthroplasty (THA), and 1 Rotator Cuff Repair. The studies utilized multiple methods of analgesic administration. For LB, the studies evaluated 4 nerve blocks – including 1 Interscalene Nerve Block (ISB), 2 Adductor Canal Blocks (ACB), and 1 Brachial Plexus Blockade (BPB), as well as 6 Periarticular Injections (PAI) and 4 Local Infiltrations (LIC). For ROPI, the studies evaluated 7 nerve blocks – 4 ISBs, 2 ACBs, and 1 BPB, as well as 6 PAIs and 2 LICs. Each study's surgical procedure and method of analgesic infiltration can also be found in Table 1, alongside OME and LOS outcomes.

Author	**Surgical / Block Site**	**Sample Size / Infiltration Sites**	**Anesthetic Dosage**		**Outcomes****	
					OME [Mean (SD)]	Hospital LOS [Mean]
Klag 2022*	TSA	N = 87 LB LIC = 26 ROPI LIC = 30 ROPI ISB = 31	LB LIC ROPI LIC ROPI ISB	266mg LB 200mg ROPI + 1mg Epinephrine + 30mg Ketorolac 200mg ROPI	POD 0-2: (NS) POD 3: 2.90 (4.13) LB LIC vs. 7.54 (10.41) ROPI LIC; (P = 0.033)	1.5 LB LIC vs. 1.07 ROPI LIC vs. 1.5 ROPI ISB; (P < .001)
Krupp 2022	TSA	N = 54 LB ISB = 21 ROPI ISB = 33	LB ROPI	133 mg LB + 50mg BUPI (Single-Injection) 100mg ROPI (Single-Injection) plus 8mg/hr. ROPI (Catheter)	POD 1: (NS) POD 2: 0.0 (0.0) LB vs. 0.64 (0.99) ROPI; P = 0.001 POD 3: (NS)	(NS)

Lo 2022	TSA	N = 112 LB LIC = 33 ROPI LIC = 37 BUPI LIC = 42	LB ROPI BUPI	266mg LB 400mg ROPI + 30ng Ketorolac + 0.6mg Epinephrine 50mg BUPI + Epinephrine and 50mg BUPI	Hospital Total: (NS)	NR
Malige 2022	TKA	N = 100 LB ACB = 50 ROPI ACB = 50	LB ROPI	266mg LB + 25mg BUPI (ACB) and 40mg ROPI (iPACK block) 50mg ROPI (ACB) and 40mg ROPI (iPACK block)	Hospital Total: 40.9 LB vs 47.3 ROPI; P = 0.038	1.51 LB vs 2.07 ROPI; (P < .01)
Simovitch 2022	Rotator Cuff Repair	N = 92 LB BPB = 46 ROPI BPB = 46	LB ROPI	133mg LB + 50mg BUPI 150mg ROPI + 8mg Dexamethasone	Daily Average: 2.8 (1.2) LB vs. 19.6 (1.2) ROPI; (P<0.001) 8-Day Average: 48.5 (1.0) LB vs. 190.1 (1.0) ROPI; (P<0.001)	NR
Ali 2021	TSA	N = 108 LB LIC = 54 ROPI ISB = 54	LB ROPI	266mg LB + 150mg BUPI-Epinephrine 50-225mg ROPI (based on BW)	POD 1: 36 (48) LB vs. 18 (12) ROPI; (P=0.01) POD 2-4: (NS)	(NS)

Hungerford 2021	TKA	N = 100 LB ACB = 46 ROPI ACB = 54	LB ROPI	133 mg LB + 65 mg BUPI 125mg ROPI	POD 1-3: (NS)	(NS)
Hyland 2019	TKA	N = 53 LB PAI = 30 ROPI PAI = 27	LB ROPI	266mg LB 40mg ROPI + 10mg Morphine + 30 mg Ketorolac + 40mg Methylprednisolone	Hospital Total: (NS)	(NS)
DeClaire 2017	TKA	N = 96 LB PAI = 47 ROPI PAI = 49	LB ROPI	LB + BUPI + Ketorolac + Morphine + Epinephrine ROPI + Ketorolac + Morphine + Epinephrine	Hospital Total: (NS)***	(NS)
Amundson 2017	TKA	N = 157 LB PAI = 52 ROPI PAI = 55 BUPI PNB = 50	LB ROPI BUPI	266mg LB + 30mg Ketorolac + 125mg BUPI + 0.125mg Epinephrine 200-400mg ROPI + 0.1-0.3mg Epinephrine + 30mg Ketorolac 20mg/hr BUPI (Femoral Nerve Catheter) and 75mg BUPI (Sciatic Nerve Single-Injection)	POD 0-2: (NS)	(NS)*

Johnson 2017	THA	N = 159	LB	266mg LB + 30mg Ketorolac + 125mg BUPI + 0.125mg Epinephrine	POD 0-2: (NS)	(NS)*
		LB PAI = 54	ROPI	200-400mg ROPI + 0.1-0.3mg Epinephrine + 30mg Ketorolac		
		ROPI PAI = 54				
		BUPI PNB = 51	BUPI	20mg/hr BUPI (Catheter) and 75mg BUPI (Injection)		
Barrington 2017	TKA	N = 119	SA+LB	9mg BUPI and 266 mg LB + 125mg BUPI + 30mg Ketorolac + 0.1mg Epinephrine	Hospital Total: (NS)	(NS)
		BUPI SA+LB PAI = 40				
		ROPI+IM SA = 41	IM SA	250mg ROPI and 9mg BUPI + 0.2-0.25mg Morphine		
		BUPI SA+ROPI PAI = 38	SA+ROPI	9mg BUPI and 250mg ROPI + 30mg Ketorolac + 0.1mg Epinephrine		
Okoroha 2016	TSA	N = 57	LB	266mg LB	POD 0: 14.8 (9.2) LB vs. 21.4 (11.3) ROPI; (P = .02)	(NS)
		LB LIC = 26	ROPI	200mg ROPI		
		ROPI ISB = 31			POD 1-3; (NS)	
Collis 2015	TKA	N = 105	LB	266mg LB	POD 1-3; (NS)***	(NS)
		LB PAI = 54				
		ROPI PAI = 51	ROPI	246.25mg ROPI + 0.5mg Epinephrine, 30mg Ketorolac + 0.08mg Clonidine		

* SD parameters are reported as 25th, 75th percentile. **All drugs are reported in Milligrams (mg) and LOS reported in days; *** Hydrocodone Equivalents; ACB: Adductor Canal Block ; ACL: Anterior Cruciate Ligament; ACLR: Anterior Cruciate Ligament Reconstruction; BPB: Brachial Plexus Blockade; BUPI: Plain Bupivacaine BW: Bodyweight; IM: Intrathecal Morphine iPACK: Infiltration between Popliteal Artery and Capsule of the Knee; ISB: Interscalene Nerve Block LB: Liposomal Bupivacaine; LIC: Local Infiltrative Cocktail LOS: Length of Stay; NS: Not Significant OME: Oral morphine equivalents (Total opioid consumption); PAI: Periarticular Injection PNB: Peripheral Nerve Block; POD: Post Operative Day ROPI: Ropivacaine; SA: Spinal Anesthesia THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty TSA: Total Shoulder Arthroplasty

Table 1: Summary of individual studies.

While not a primary outcome, if studies reported their associated costs of ROPI vs LB use, the information was compiled in Table 2 and their findings summarized in this section. If study costs were reported but were not directly related to the price of LB or ROPI (e.g., physician fees, other medical equipment), the information was not included. In addition, GRADE review results can be found in Table 3.

Author	**Anesthetic Price**	
	LB	**ROPI**
Klag 2022	$315	$24.68 (Cocktail)
Lo 2022	$434.96	$21.95 (Cocktail)
Hungerford 2021	$180.35	$4.42 (Injection)
Hyland 2019	$300.66	$16.83 (Cocktail)
Declaire 2017	$311.85	$11 (Injection)
Barrington 2017	$315	$20 (Cocktail)
Collis 2015	$285	$40 (Cocktail)

Table 2: Cost of LB and ROPI.

Effect measure (endpoint)	Study Design	No. of Studies	No. of Patients [References]		Certainty of Scientific Evidence	Comments
			LB	ROPI		
LB decreases OME (Klag, Krupp, Malige, Simovitch & Okoroha)	4 RTC & 1 Prospective Cohort Study	5	169	190	Low: ⊕⊕○○	Reduction for Study design, Indirectness & Imprecision
LB has no effect on OME (Lo, Hungerford, Hyland, Amundson, DeClaire, Johnson, Barrington, Collis)	8 RTC	8	356	365	Moderate: ⊕⊕⊕○	Reduction for Imprecision
LB increases OME (Ali)	1 RTC	1	54	54	Very low: ⊕○○○	Reduction for Study design, Indirectness, Imprecision & Only study
LB decreases LOS (Malige)	1 RTC	1	50	50	Very low: ⊕○○○	Reduction for Study design, Imprecision & Only study

LB has no effect on LOS (Krupp, Ali, Hungerford, Hyland, Amundson, DeClaire, Johnson, Barrington, Okoroha, Collis)	10 RTC	10	424	446	Moderate: ⊕⊕⊕○	Reduction for Study design
LB increases LOS (Klag)	1 Prospective Cohort Study	1	26	30	Very low: ⊕○○○	Reduction for Study design, Imprecision & Only study

Table 3: GRADE Score Summary.

Postoperative OME Use

6 of the 14 included studies found significant differences in postoperative OME between LB and ROPI groups. Five of these 6 studies reported a reduced postoperative OME use in patients treated with LB. Malige et al. reported LB-treated patients required less postoperative OME use throughout their hospital stay compared to those given ROPI. [24] Simovitch et al. found that, following rotator cuff repair procedure, the LB group had lower OME requirements each day for a total of eight days. [25] Okoroha et al. found LB participants required less OME only on postoperative day (POD) zero. [26] Krupp et al. found the LB group required less OME only on POD 2 compared to the ROPI group. [27] Klag et al. reported significantly less OME use in the LB group only on POD 3. [28] Contrary to the above five studies, Ali et al. found that ROPI reduced postoperative OME use on POD 1. [29] Collectively, these studies had a low or very low level of scientific certainty. The remaining eight studies reported no difference in post-operative OME requirements and scored a moderate level of scientific certainty (Table 1) [30-37].

Postoperative LOS

12 out of the 14 studies reported postoperative LOS. Among these 12 studies, two studies found a significant effect on LOS either by LB or ROPI. Malige et al. reported a 13-hour decrease in LOS in patients treated with LB (36.3 vs 49.7 hours with ROPI; $p<0.01$). [24] However, Klag et al. found that patients receiving ROPI experienced a significantly reduced LOS by about half day (1.07 vs. 1.5 days with LB; $p<0.001$). [28] Both studies, on review, were determined to be low quality studies. The remaining 10 studies demonstrated comparable postoperative LOS between the two treatments and were determined to have a moderate level of scientific certainty. [26,27,29-36] Two studies did not report LOS (Table 1) [25,37].

Cost of LB and ROPI

LB was consistently more expensive than ROPI in every study that reported costs. LB was found to cost 20 to 30 times more than ROPI. This remained true even when accounting for studies which used ROPI cocktails, where ROPI was mixed with other ingredients that made the product more expensive than if ROPI were used alone (Table 2).

GRADE Scores

The GRADE scores are summarized in Table 3. GRADE scores for individual studies can be found in the supplementary table. The 5 studies with LB reducing OME requirements were found to be of low quality by GRADES metrics. Four of these studies did not blind the participants. [25,27,28,30] One study included chronic opioid users only in the cohort that received ROPI but none in LB group, thus introducing bias. [28] Krupp et al. [27] and Okoroha et al. [26] also used different infiltration sites and mechanisms of administration in their LB vs. ROPI comparison trials, introducing indirectness between study group outcomes, as the treatments were not equivalent. Ali et al. was the only study to report the use of LB increased OME requirements, therefore demonstrating inconsistency as it was the only study to report this outcome. In addition, the study was not blinded to the participants, and used both different infiltration sites and different mechanisms of analgesic application. [29] It was determined to be very low quality by GRADE metrics.

Author	Study Design	Publication	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty of Scientific Evidence
Klag 2022	Prospective Cohort Study	Sage Journals: Shoulder & Elbow	**Serious** Not Patient-Blinded 9 patients (31%) were using opioid pain medication for at least three months prior to their surgery in ROPI group compared to zero patients in the LB group	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Low: ⊕⊕○○
Krupp 2022	RCT	Archives of Orthopaedic and Trauma Surgery	**Serious** Not Patient-Blinded Demographic Bias: LB Group = 2:1 Male-Female ratio ROPI Group = 1:1 Male-Female ratio	**Not Serious**	**Serious** ROPI group contains continuous indwelling catheter while the LB did not	**Serious** Large OME confidence Intervals	Very low: ⊕○○○
Lo 2022	RCT	Seminars in Arthroplasty: JSES	**Not Serious**	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○
Malige 2022	RCT	The Journal of Arthroplasty	**Not Serious**	**Not Serious**	**Serious** Low ROPI dosage compared to other studies	**Serious** Large OME confidence Intervals	Low: ⊕⊕○○
Simovitch 2022	RCT	JB & JS Open Access	**Serious** Not Patient-Blinded	**Serious** Results drastically differ from every other study	**Not Serious**	**Not Serious**	Low: ⊕⊕○○
Ali 2021	RCT	Journal of Shoulder and Elbow Surgery	**Serious** Not Patient-Blinded Dr. Srikumaran received personal fees from Pacira Pharmaceuticals (Producers of LB)	**Not Serious**	**Serious** Compared LB LIC vs. ROPI ISB	**Serious** Large OME confidence Intervals	Very low: ⊕○○○

Hungerford 2021	RCT	The Journal of Arthroplasty	**Not Serious**	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○
Hyland 2019	RCT	The Journal of Arthroplasty	**Not Serious**	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○
Amundson 2017	RCT	Anesthesiology	**Serious** Not Patient-Blinded Dr. Pagnano is Pacira Pharmaceuticals (Producers of LB) consultant	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Low: ⊕⊕○○
DeClaire 2017	RCT	The Journal of Arthroplasty	**Serious** Dr. DeClaire received research funding from Pacira Pharmaceuticals (Producers of LB)	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○
Johnson 2017	RCT	The Journal of Bone and Joint Surgery	**Serious** Not Patient-Blinded Dr. Pagnano is Pacira Pharmaceuticals (Producers of LB) consultant	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Low: ⊕⊕○○
Barrington 2017	RCT	Clinical Orthopaedics and Related Research	**Serious** All the authors were paid by Pacira Pharmaceuticals (Producers of LB)	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○
Okoroha 2016	RCT	Journal of Shoulder and Elbow Surgery	**Serious** Not Patient-Blinded	**Not Serious**	**Serious** Compared LB LIC vs. ROPI ISB	**Serious** Large OME confidence Intervals	Very low: ⊕○○○

Collis 2015	RCT	The Journal of Arthroplasty	**Not Serious**	**Not Serious**	**Not Serious**	**Serious** Large OME confidence Intervals	Moderate: ⊕⊕⊕○

Supplementary Table: GRADE score of individual study.

The studies that demonstrated difference in LOS were also both found to be low quality by the GRADEs metric. Malige et al. demonstrated inconsistency – heterogeneity with other results – as it was that only study that reported a decrease in hospital LOS for patients treated with LB. In addition, the study did not have equivalent anesthetic dosage between the LB and ROPI groups. [24] Klag et al. was the only study to show LB increased postoperative LOS. However, the trial was not blinded to the participants and was ranked low quality by GRADE metrics.[28] When comparing LB and ROPI, 10 studies reported statistically equivalent hospital LOS and 8 studies reported equivalent OME requirements. These studies were given a moderate level of scientific certainty by GRADEs metrics. These studies were shown to have no significant sources of bias, inconsistency, indirectness, or imprecision. Five studies [29-31,33,36] listed Parica Pharmaceuticals, the manufacturer of LB, as a funding source for their trials. However, because these studies consistently showed no significant findings in favor of LB regarding the literature review primary outcomes of OME and LOS, we chose not to include this as a source of bias. For example, Ali et al. disclosed that they were paid personal fees from Parica Pharmaceuticals and reported that LB actually increased OME use postoperatively [29].

Discussion

The rising incidence of opioid use disorder and subsequent risk of overdose is an ongoing crisis. The United States accounts for a disproportionate amount of the world's opioid consumption, utilizing about 80% of the global supply for less than 5% of the global population. [38] Orthopedists rank third among physicians for highest prescriber of opioids. [39] Therefore, there is compelling evidence to establish alternative pain management strategies other than opioid analgesics. LB, as nerve blocks or local surgical site infiltration, has been proposed as one such alternative analgesic for postoperative pain control, and as such, it is important to determine whether its use can effectively reduce postoperative opioid use. Moreover, given that LB is more expensive than other long-acting local anesthetics, e.g., ROPI, the price could be offset if it significantly reduced postoperative pain and subsequently, reduced hospital LOS. However, in this systematic review of published RCTs and prospective studies, LB did not show superiority to ROPI in terms of postoperative use of narcotics and LOS. When factoring in cost, this review supports ROPI as the most cost-effective means for local analgesia during operations. On systematic review of the literature, LB does not significantly reduce OME or LOS compared to ROPI. These findings remained consistent across multiple surgical procedures (e.g., TSA, TKA, etc.) and multiple modalities of use (e.g., PNB, PAI, ISB, local, etc.). Across 14 prospective and RCT studies, we found that LB and ROPI were equivalent in managing postoperative pain. 8 of the 14 trials reported equal efficacy between LB and ROPI as determined by OME use post-procedure and 10 of the 14 trials reported there was no significant change in LOS postoperatively, with a composite moderate certainty of evidence for each outcome. Of the 6 studies that showed better OME outcomes for either LB or ROPI, the improvement was not consistent across the study timeline. For example, Okoroha et al. found that LB patients required less OME analgesics only for the POD 0 but not the following postoperative days. [26] Similarly, Krupp et al. found that LB reduced OME use only on POD 2 compared to ROPI and not on POD 1 or POD 3. [27] Klag et al. found that ROPI reduced OME use only on POD 3 but not on the previous or following postoperative days. [28] Furthermore, when analyzing the LOS data, the differences in LOS was at most half a day. Even among the studies that did report that ROPI or LB reduced OME requirements at some timepoint within their study, the benefit did not result in reduced LOS. Overall, all studies that did demonstrate a difference in OME or LOS were found to be of low or very low quality per our criteria. It is important to additionally note that the OME analgesics delivered to each participant may be largely influenced by metrics other than patient pain. Opioids received by a patient may be influenced by insurance, hospital policy, and even the individual prescriber's outlook on pain management. DeMaio et al. compared ACBs of ROPI and LB for participants undergoing anterior cruciate ligament reconstruction and found that OME analgesia data collected could not result in conclusive findings as the opioids administered were a function of hospital management's desire to reduce opioid consumption, rather than a reflection of patient pain. [40] Since the paper did not report on LOS and did not end up including their OME outcomes as valid, they were ultimately excluded from our review. Nevertheless, this factor is still an important consideration when evaluating the results of any of the studies in this literature review.

One consistent result throughout the study was that LB was significantly more expensive. This remained true across multiple methods of administration, and only veered in cases where physician's fees or indwelling catheters were added. [26,27] With such limited findings on the efficacy of LB's ability to reduce hospital costs or opioid dependency for patients when compared with ROPI, it brings into question whether hospitals, physicians, insurance companies, and most importantly patients should be spending such an increased amount on a drug without proven additional benefit. Hamilton et al. conducted a health economics analysis on their RCT comparing LB to BUPI evaluating post-trial cost utility. The study conducted participant follow up via self-reported data on the use of social services, health care costs, and hospital readmissions and reported no differences in any of these outcomes between the two drugs. [41] We are not aware of the existence of a similar cost analysis study comparing ROPI and LB, but this would be an important area of future research as it is of both clinical and financial importance. To our knowledge, this is the only comprehensive literature review comparing LB and ROPI, as opposed to LB and BUPI. In addition, this is the only literature review that we know of that considers the price point variance for the two analgesics and then analyzes outcomes which modify costs. While in this case it was not a large price point modifier, in other situations this methodology would be useful, as LOS and OME have important sociological and economic impacts on patients, hospitals and the general public. If a drug was found to be expensive, but significantly reduced LOS and OME requirements, thus minimizing the addictive potential of opioids, it would certainly be worth the economic expense from an administrative, patient, and societal standpoint. However, based on current literature, this is not the case for LB.

Our review does have some limitations. We consulted four databases, and we limited our search to only English language articles. In addition, we limited the reported outcomes of the study to LOS and OME and did not report on other important postprocedural metrics such as patient reported pain scores or time to walking. A post-hoc evaluation of LB vs ROPI RCTs on clinicaltrials.gov found that those trials which reached completion largely reported equal efficacy of LB and ROPI, even when using metrics other than OME and LOS as outcomes, further strengthening the confidence in our results. Another limitation of this literature review is the inclusion of studies which compared LB vs ROPI using multiple techniques of administration. Comparing two drugs, while using different mechanisms of application for each one makes the significance of the findings of that trial less statistically powerful. To account for this inequivalence, we added a GRADE criterion for this factor and scored those studies lower. That said, every technique comes with inherent advantages and disadvantages. In incorporating multiple administrative techniques, both in what was compared within individual studies and what was collected for our review, we have created a holistic evaluation by involving many permutations of use comparing LB and ROPI. Therefore, the use of different mechanisms of administration strengthens the generalizability of our literature review findings – that LB does not reduce postoperative OME requirements or LOS compared to ROPI.

Conclusion

The use of opioids for management of post procedure pain is currently a standard practice, yet discussions surrounding opioid mitigation strategies to curb addiction potential are increasing. Insufficient pain management is associated with increased morbidity, functional and quality-of-life impairment, delayed recovery time, prolonged duration of opioid use, and higher health-care costs. [42] Multimodal analgesia, including intra-operative nerve blocks, are an option for reducing opioid pain management. The advent of expensive liposomal formulations, such as LB, which claim to provide extended-release analgesia, raise the question of whether these will improve multimodal analgesia practices and reduce patient pain over current long-acting local analgesic adjuncts. A pharmaceutical product that reduced opioid reliance postoperatively would have merits sociologically, and if pain outcomes were improved enough to shorten patient LOS, also prove financially beneficial. However, this review found that LB is not superior to ROPI in terms of patient OME requirements after their procedures, nor did the use of LB modify postoperative hospital LOS. Ultimately, the results of this review do not report significant outcome differences and cannot justify the significant cost of LB.

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