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ORIGINAL ARTICLE

The postoperative analgesic efficacy of liposomal bupivacaine versus long-acting local anaesthetics for peripheral nerve and field blocks

A systematic review and meta-analysis, with trial sequential analysis

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BACKGROUND Liposomal bupivacaine is claimed by the manufacturer to provide analgesia for up to 72 h postoperatively.

OBJECTIVES To compare the postoperative analgesic efficacy of liposomal bupivacaine versus long-acting local anaesthetics for peripheral nerve or field blocks.

DESIGN A systematic review and meta-analysis with trial sequential analysis.

DATA SOURCES MEDLINE, Embase and Web of Science, among others, up to June 2022.

ELIGIBILITY CRITERIA We retrieved randomised controlled trials comparing liposomal bupivacaine versus bupivacaine, levobupivacaine or ropivacaine for peripheral nerve and field blocks after all types of surgery. Our primary endpoint was rest pain score (analogue scale 0 to 10) at 24 h. Secondary endpoints included rest pain score at 48 and 72 h, and morphine consumption at 24, 48 and 72 h.

RESULTS Twenty-seven trials including 2122 patients were identified. Rest pain scores at 24 h were significantly reduced by liposomal bupivacaine with a mean difference (95% CI) of -0.9 (-1.4 to -0.4), $I^2 = 87\%$, $P < 0.001$. This reduction in pain scores persisted at 48 h and 72 h with mean differences (95% CI) of -0.7 (-1.1 to -0.3), $I^2 = 82\%$, $P = 0.001$ and -0.7 (-1.1 to -0.3), $I^2 = 80\%$, $P < 0.001$, respectively. There were no differences in interval morphine consumption at 24 h ($P = 0.15$), 48 h ($P = 0.15$) and 72 h ($P = 0.07$). The quality of evidence was moderate.

CONCLUSIONS There is moderate level evidence that liposomal bupivacaine reduces rest pain scores by 0.9 out of 10 units, when compared with long-acting local anaesthetics at 24 hours after surgery, and by 0.7 up to 72 hours after surgery.

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KEY POINTS

- Liposomal bupivacaine is claimed by the manufacturer to provide analgesia for up to 72 h postoperatively.
- We undertook a systematic review and meta-analysis with trial sequential analysis to compare the postoperative analgesic efficacy of liposomal bupivacaine versus long-acting local anaesthetics for peripheral nerve and field blocks.
- We analysed all randomised controlled trials comparing liposomal bupivacaine versus bupivacaine, levobupivacaine or ropivacaine for peripheral nerve blocks after all types of surgery.
- Liposomal bupivacaine statistically reduces pain scores at 24, 48 and 72 postoperative hours, but without clinical relevance.

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Introduction

Optimal pain control in the postoperative period remains challenging.[1] When long-acting local anaesthetic molecules are combined with pharmacological adjuncts such as dexamethasone, the duration of analgesia after administration of local anaesthetics near peripheral nerves may last up to 24 h.[2–4] To prolong the analgesia beyond 24 h, insertion of a perineural catheter with a continuous infusion of local anaesthetics is a frequently used option. However, the procedure is time-consuming, requires specific technical skills and necessitates a complex and costly logistic organisation for follow-up, while, at the same time, the catheters are prone to migration, spontaneous dislodgement, and leakage, leading to a nonnegligible rate of secondary failure.[5]

Another option to prolong analgesia beyond 24 h is the injection of liposomal bupivacaine: the manufacturer claims an efficacy lasting up to 72 h. Liposomal bupivacaine is a sustained-release multivesicular formulation of bupivacaine, which is currently approved by the United States Food and Drug Administration for wound infiltration and interscalene brachial plexus block,[6] and by the European Medicines Agency for brachial plexus, femoral nerve and field blocks.[7]

Two previous meta-analyses investigated the analgesic efficacy of liposomal bupivacaine when compared with an active drug group for peripheral nerve blocks, but were limited by two factors.[8,9] First, these two publications did not include articles comparing liposomal bupivacaine with levobupivacaine or ropivacaine,[8,9] and second, one of them did not include studies investigating field blocks and included only five controlled trials published as full-text.[8]

As additional studies have been published since these two meta-analyses, and as bupivacaine, levobupivacaine and ropivacaine are all long-acting local anaesthetics with similar durations of analgesia, we undertook this systematic review and meta-analysis with trial sequential analysis with the objective of providing a more comprehensive understanding of the postoperative analgesic efficacy of liposomal bupivacaine for peripheral nerve and field blocks when compared with long-acting local anaesthetics.

Materials and methods

Literature search and inclusion criteria

This investigation was conducted following the recommended process from the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement[10] and was prospectively registered through the International Prospective Register of Systematic Reviews (registration number CRD42021291745).

The following electronic sources were searched up to 30 June 2022: MEDLINE, Embase, CINHAL, Cochrane Central Register of Controlled Clinical Trials, Web of Science and ProQuest Theses. The intervention search terms applied were Liposome bupivacaine OR Liposomal bupivacaine OR liposome OR Exparel. Among others, the following words were searched as keywords: Liposom*, Lipob*. Deduplication of the retrieved records was done manually. Population limits were then applied including Clinical trials OR Random allocation OR Therapeutic use. Details of this literature search are provided in the supplementary document 1, http://links.lww.com/EJA/A821.

Search results were independently screened by two authors (AN and MG) using the title and the abstract. Only randomised controlled trials on adult patients were included, without language restriction. The full texts of potentially eligible articles were subsequently evaluated for inclusion. Discrepancies were resolved by discussion until consensus was reached or, if needed, involvement of the senior author (EA). Finally, after compiling the results of the above search, the authors independently reviewed the references from all included trials for any applicable articles that were not captured by the described approach.

Population

The meta-analysis addresses adult patients undergoing any type of surgery with a peripheral nerve or field block.

Intervention and comparator

Only randomised controlled trials investigating pain outcomes and comparing liposomal bupivacaine with any type of long-acting local anaesthetic (bupivacaine, levobupivacaine, ropivacaine), combined or not with perineural adjuncts, were included in this meta-analysis.

Outcomes

Defined outcomes were extracted from each article following our routine approach previously described in meta-analyses on acute postoperative pain.[11,12] The primary outcome was the pain score at rest at 24 postoperative hours. Secondary outcomes were rest pain scores at 2, 48 and 72 postoperative hours; interval morphine consumption at 24, 48 and 72 postoperative hours; presence of nausea or vomiting at 24, 48 and 72 postoperative hours; and hospital length of stay. Additional outcomes were incidences of LAST (local anaesthetic systemic toxicity) and nerve injury.

Trial characteristics

Extracted trial characteristics were: type of surgery; technique of peripheral nerve or field block; anaesthetic strategy; concentration, volume and type of local anaesthetic administered; postoperative analgesic regimen; and whether a conflict of interest was declared or not (study sponsored by the industry or one of the authors received honorarium from Pacira BioSciences, Pacira BioSciences. (USA).

Rating of the studies

The Cochrane Collaboration's Risk of Bias Tool[13] was applied to each randomised trial in order to evaluate the methodologic quality. Two authors (AN and MG) independently reviewed and scored the items from this tool for each trial. The senior author (EA) adjudicated disagreements during the initial assessment.

Data extraction

The texts, tables or images from the included trials were assessed to extract the number of participants, number of events, means, standard deviations, standard error of means and 95% confidence intervals (CIs). If an included trial did not indicate the sample size or failed to describe the results as a mean and standard deviation or standard error of the mean and 95% CI, we attempted to contact the corresponding author three times via e-mail. We requested access to the missing data or alternately to the complete dataset, and if we were unable to obtain these additional elements, we employed the median and interquartile range as approximations of the mean and standard deviation, by estimating the mean as equivalent to the median, and the standard deviation as the interquartile range divided by 1.35 or the range divided by 4.[13] If needed, data were extracted from figures using Plotdigitizer (https://plotdigitizer.com). All opioids were converted to equianalgesic intravenous (i.v.) morphine doses (i.v. morphine 10 mg = oral morphine 30 mg = i.v. tramadol 100 mg = i.v. pethidine 75 mg = i.v. fentanyl 100 μg = i.v. nalbuphine 10 mg = oral hydrocodone 30 mg = oral oxycodone 30 mg = oral codeine 165 mg).[2] For pain scores reported on a 0 to 10 verbal, visual or numeric rating scale, we accepted these as analogue data for the purpose of statistical evaluation. When maximum and minimum pain scores were given, we elected to include the minimum pain score. Finally, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system was used to evaluate the quality of evidence for each reported outcome.

Statistical analysis

All meta-analyses were conducted using the Review Manager (RevMan, Computer program, version 5.4, The Cochrane Collaboration, 2020). For continuous data, this software estimates the weighted mean differences, and similarly the risk ratio for categorical data between groups, with an overall estimate of the pooled effect. If two or more included trials presented an outcome, we conducted a meta-analysis. We set predetermined limits for low (25 to 49%), moderate (50 to 74%) and high (≥75%) heterogeneity based on the calculated I^2 coefficient.[14] A random effects model was employed when heterogeneity was found to be moderate or high; otherwise, a fixed effects model was applied.[15]

To account for potential contributors to heterogeneity, we performed subgroup analyses for our primary outcome (rest pain score at 24 postoperative hours) according to the type of block (peripheral nerve versus field blocks), the nerve block technique (ultrasound versus nerve stimulation), the dose of liposomal bupivacaine administered (doses ≤ 133 mg versus doses from 134 to 266 mg), the comparator (bupivacaine, levobupivacaine or ropivacaine), the combination or not with adjuncts other than epinephrine, the anaesthetic strategy (general versus spinal anaesthesia or no additional anaesthesia), the presence of baseline analgesia defined as the prescription of two nonopioid analgesics and whether a conflict of interest was declared or not.

The risk of publication bias associated with the primary outcome was estimated by drawing a funnel plot of the mean difference standard error of rest pain score at 24 postoperative hours (y-axis) as a function of the mean difference of rest pain score at 24 postoperative hours (x-axis)[16] and confirmed with Duval and Tweedie's trim and fill test.[17] This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, New Jersey, USA). Finally, trial sequential analysis was performed on the primary outcome to confirm whether firm evidence was reached or not (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

We present results as the mean difference or relative risk with 95% confidence interval and a two-sided P value less than 0.05 was deemed to be significant.

Results

Of the 1996 trials identified from the literature search, 27 met the inclusion criteria,[18–44] accounting for a total of 2122 patients. Figure 1 presents the PRISMA flow diagram showing the literature search results and Fig. 2 summarises the risk of bias of the different trials. Seventeen authors were contacted[18,21–24,26–28,30,31,34,35,37–40,43] and five provided additional data.[18,21,23,26,27]

Trial characteristics

Table 1 presents the trial characteristics. Eleven trials included patients undergoing orthopaedic surgery,[18,20,24,27–29,32,33,35,36,38] six others included patients undergoing breast or gynaecological surgery,[21,23,26,30,34,44] six trials included patients undergoing abdominal surgery[22,25,31,37,41,43] and four trials included patients who underwent other types of surgery.[19,39,40,42] Fifteen trials investigated the efficacy of liposomal bupivacaine on peripheral nerve blocks,[18–21,24,27–29,32,33,36,38–40,42] while 12 explored its efficacy on field blocks.[22,23,25,26,30,31,34,35,37,41,43,44] Nerve block were performed under ultrasound guidance in 19 trials [18,20,22–24,27–36,38,39,43,44] and following anatomic landmarks in four studies[19,21,25,42]; in another four studies,[26,37,40,41] the surgeon performed the block under

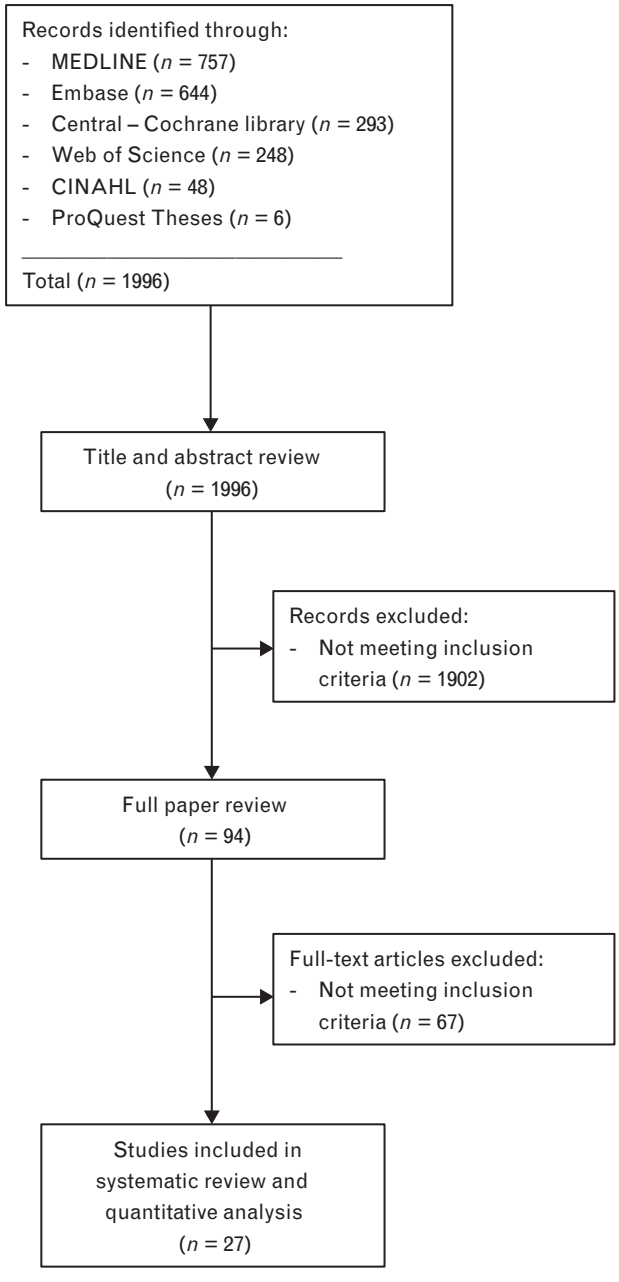

Fig. 1 PRISMA flow diagram showing literature search results. Twenty-seven randomised controlled trials were included in the analysis.

direct vision. Liposomal bupivacaine doses ranged from 65[39] to 266 mg.[22,23,25,26,28,33,35,37,41–44] Of note, 12 trials[21,24,27,29,32,33,35–39,43] combined liposomal bupivacaine with bupivacaine, six[23,26,30,31,42,44] with 0.9% saline, and four with both. Plain bupivacaine was the active comparator in all trials, except four where ropivacaine was administered[20,33,36,42]; no trials injected levobupivacaine. The local anaesthetic was mixed with dexamethasone in four studies,[18,32,36,43] with epinephrine in two studies[34,40] and with both in another study.[37] The peripheral nerve block was combined with a general anaesthesia in 23 studies[18–27,30–32,34–38,40–44] and with a spinal anaesthesia in two studies[29,33]; the anaesthetic strategy was not specified in two trials.[28,39] Fourteen trials prescribed a multimodal analgesic regimen for the postoperative period.[20–22,24,29,32,33,36–41,43] Finally, nine trials declared a conflict of interest.[22,24,27,29–31,38–40]

Primary outcome

On the basis of 22 trials with a total of 1636 patients,[18,19,21–24,26–32,35–40,42–44] the pain score at rest at 24 postoperative hours was significantly reduced in patients receiving liposomal bupivacaine. For both types of block combined, the mean difference (95% CI) was -0.9 (-1.4 to -0.4), $I^2 = 87\%$, $P < 0.001$. When analysed by subgroup, there was no difference in the field block group; there was a significant difference between the block groups ($P = 0.03$, Fig. 3). There was also a subgroup difference in doses of liposomal bupivacaine administered with a higher mean difference in the low-dose group (up to 133 mg: mean difference (95% CI) of -1.3 (-2.2 to -0.5), $I^2 = 91\%$, $P = 0.002$; 134 to 266 mg: mean difference (95% CI) of -0.3 (-0.5 to -0.1), $I^2 = 0\%$, $P = 0.01$; subgroup difference: $P = 0.01$). On the contrary, there was no subgroup difference when our primary outcome was analysed according to the nerve block technique ($P = 0.29$), type of local anaesthetics ($P = 0.28$), the combination or not with adjuncts ($P = 0.46$), the anaesthetic strategy ($P = 0.05$), the presence of baseline analgesia ($P = 0.61$) or whether a conflict of interest was declared or not ($P = 0.35$). The trial sequential analysis indicated that firm evidence was reached regarding the superiority of liposomal bupivacaine over the other long-acting local anaesthetics (supplementary Figure 1, http://links.lww.com/EJA/A820). The funnel plot reveals absence of risk of publication for the primary outcome (supplementary Figure 2, http://links.lww.com/EJA/A820), confirmed with the Duval and Tweedie's Trim and Fill test; with a random effects model: this test calculated the point estimate for the combined studies to be -0.40 (95% CI: -0.64 to -0.16); using Trim and Fill, these values were unchanged, suggesting that no studies are missing.

Secondary outcomes

Pain scores at rest at 48 and 72 postoperative hours were also significantly reduced, as opposed to the majority of the other secondary outcomes (Table 2). Two trials looked at the incidence of LAST and reported none[23,39]; no trials investigated the incidence of nerve injury.

Quality of evidence

According to the GRADE system, the quality of evidence was moderate for our primary and secondary outcomes (Table 3).

Table 1 Study characteristics

Reference	Group (*n*)	Surgery	Intervention					Minimal clinically important difference defined by the authors
			Peripheral nerve block, technique	Anaesthetic strategy	Liposomal Liposomal bupivacaine	Long-acting local anaesthetics	Postoperative analgesic regimen	
Baessler *et al.* [18]	Liposomal ($n=26$) Control ($n=26$)	Rotator cuff repair	Interscalene brachial plexus block, US	General anaesthesia	1 : 1.5 : 0.5 Liposomal bupivacaine, bupivacaine 0.5% and normal saline, 30 ml, with dexamethasone 4 mg	Bupivacaine 0.5%, 30 ml, with dexamethasone 4mg	Oxycodone	1.4 units in rest pain score (time interval not specified)
Cox *et al.* [19]	Liposomal ($n=24$) Control ($n=24$)	Ocular evisceration	Retrobulbar nerve block, landmark	General anaesthesia	Liposomal bupivacaine, 10 ml	Bupivacaine 0.75%, 6 ml	Acetaminophen, oxycodone	Not specified
Dawes *et al.* [20]	Liposomal ($n=56$) Control ($n=58$)	Total shoulder arthroplasty	Interscalene brachial plexus block, US	General anaesthesia	Liposomal bupivacaine, 6 ml	Ropivacaine 0.5%, 20 ml	Acetaminophen, NSAID, tramadol	1.4 units in rest pain score (time interval not specified)
Dengler *et al.* [21]	Liposomal ($n=60$) Control ($n=60$)	Posterior colporraphy	Pudendal nerve block, landmark	General anaesthesia	1 : 1 Liposomal bupivacaine / bupivacaine 0.25%, 20 ml	Bupivacaine 0.25%, 20 ml	Acetaminophen, NSAID, oxycodone	Not specified
Fafaj *et al.* [22]	Liposomal ($n=57$) Control ($n=55$)	Abdominal wall reconstruction	TAP block, US or direct visualisation by surgeon	General anaesthesia	1 : 3:2 Liposomal bupivacaine, bupivacaine 0.2% and normal saline, 120 ml	1 : 1 Bupivacaine 0.25%, and normal saline 120 ml	Acetaminophen, gabapentin, oxycodone, PCA of hydromorphone	30% reduction in opioid consumption at 72 h
Fidkowski *et al.* [23]	Liposomal ($n=27$) Control ($n=25$)	Open abdominal hysterectomy	TAP block, US	General anaesthesia	1 : 2 Liposomal bupivacaine and normal saline, 60 ml	Bupivacaine 0.25%, 60 ml	NSAID, oral opioid, PCA of morphine	35% reduction in opioid consumption at 72 h
Flaherty *et al.*[24]	Liposomal ($n=35$) Control ($n=35$)	Rotator cuff repair	Interscalene brachial plexus block, US	General anaesthesia	1 : 1 Liposomal bupivacaine / bupivacaine 0.5%, 20 ml	Bupivacaine 0.5%, 20 ml	Acetaminophen, NSAID, oxycodone	1.4 units in rest pain score (time interval not specified)
Guerra *et al.* [25]	Liposomal ($n=50$) Control ($n=50$)	Laparoscopic colorectal surgery	TAP block, landmark	General anaesthesia	1 : 2:1 Liposomal bupivacaine, bupivacaine 0.2% and normal saline, 80 ml	Bupivacaine 0.25%, 80 ml	Hydromorphone, morphine	Not specified
Ha *et al.* [26]	Liposomal ($n=22$) Control ($n=22$)	Breast reconstruction	TAP block, direct visualisation by surgeon	General anaesthesia	2 : 1 Liposomal bupivacaine and normal saline, 30 ml	Bupivacaine 0.25%, 30 ml	Oxycodone, hydromorphone	20 mg in opioid consumption (time interval not specified)
Hattrup *et al.* [27]	Liposomal ($n=52$) Control ($n=52$)	Total shoulder arthroplasty	Interscalene brachial plexus block, US	General anaesthesia	1 : 1.5 Liposomal bupivacaine, bupivacaine 0.375%, 25 ml	Bupivacaine 0.5%, 20 ml	Acetaminophen, oxycodone, tramadol, fentanyl	2 units in rest pain score (time interval not specified)
Hubler *et al.* [28]	Liposomal ($n=31$) Control ($n=32$)	Total knee arthroplasty	Adductor canal block, US	Not specified	Liposomal bupivacaine, 20 ml	Bupivacaine 0.5%, 20 ml	NSAID, oxycodone, hydromorphone	0.9 units in rest pain score (time interval not specified)
Hungerford *et al.* [29]	Liposomal ($n=46$) Control ($n=54$)	Total knee arthroplasty	Adductor canal block, US	Spinal anaesthesia	1 : 1.5 Liposomal bupivacaine, bupivacaine 0.5%, 25 ml	Bupivacaine 0.5%, 25 ml	Acetaminophen, NSAID, oxycodone	1 unit in rest pain score (time interval not specified)
Hutchins *et al.*[30]	Liposomal ($n=28$) Control ($n=30$)	Robotic assisted hysterectomy	TAP block, US	General anaesthesia	1 : 2 Liposomal bupivacaine and normal saline, 30 ml	Bupivacaine 0.25%, 30 ml	Hydromorphone, fentanyl	Not specified
Hutchins *et al.*[31]	Liposomal ($n=30$) Control ($n=29$)	Laparoscopic nephrectomy	TAP block, US	General anaesthesia	1 : 2 Liposomal bupivacaine and normal saline, 30 ml	Bupivacaine 0.25%, 30 ml	NSAID, oxycodone, hydromorphone, morphine, fentanyl	Not specified
Kim *et al.*[32]	Liposomal ($n=55$) Control ($n=56$)	Shoulder surgery	Interscalene brachial plexus block, US	General anaesthesia	2 : 1 Liposomal bupivacaine and bupivacaine 0.5%, 15 ml	Bupivacaine 0.5%, 15 ml, with dexamethasone 4 mg	Acetaminophen, NSAID, oxycodone, tramadol, hydromorphone	1.3 units in rest pain score (time interval not specified)

Table 1 (*continued*)

Reference	Group (*n*)	Surgery	Peripheral nerve block, technique	Anaesthetic strategy	Intervention Liposomal Liposomal bupivacaine	Long-acting local anaesthetics	Postoperative analgesic regimen	Minimal clinically important difference defined by the authors
Malige *et al.*[33]	Liposomal ($n=50$) Control ($n=50$)	Total knee arthroplasty	Adductor canal block, US	Spinal anaesthesia	2 : 0.5 Liposomal bupivacaine, bupivacaine 0.5%, 25 ml	Ropivacaine 0.2%, 25 ml	Acetaminophen, gabapentin, hydromorphone, methocarbamol	28% reduction in rest pain score (time interval not specified)
Motakef *et al.*[34]	Liposomal ($n=12$) Control ($n=12$)	Breast reconstruction	Interpectoral plane block, US	General anaesthesia	Liposomal bupivacaine, 10 ml	Bupivacaine 0.25% with epinephrine 5 μg ml^{-1}, 20 ml	Acetaminophen, hydrocodone, hydromorphone	Not specified
Purcell *et al.*[35]	Liposomal ($n=33$) Control ($n=37$)	Hip arthroscopy	Fascia iliaca block, US	General anaesthesia	1 : 1 Liposomal bupivacaine, and bupivacaine 0.5%, 40 ml	Bupivacaine 0.25%, 20 ml	Oxycodone, NSAID, opioid	2 units in rest pain score (time interval not specified)
Simovitch *et al.*[36]	Liposomal ($n=45$) Control ($n=44$)	Arthroscopic rotator cuff	Interscalene brachial plexus block, US	General anaesthesia	1 : 1 Liposomal bupivacaine, and bupivacaine 0.5%, 20 ml	Ropivacaine 0.5%, 30 ml, with dexamethasone 8 mg	Acetaminophen, NSAID, oxycodone/ acetaminophen, hydrocodone/ acetaminophen	1 unit in rest pain score (time interval not specified)
Truong *et al.*[37]	Liposomal ($n=51$) Control ($n=50$)	Minimal invasive colorectal surgery	TAP block, direct visualisation per surgery	General anaesthesia	2 : 1 Liposomal bupivacaine and bupivacaine 0.5%, 30 ml	1 : 1 Bupivacaine 0.25% with epinephrine 2.5 μg ml^{-1}, 30 ml, with dexamethasone 8 mg	Acetaminophen, NSAID, oxycodone, gabapentin, tramadol, opioid	15 mg in opioid consumption at 48 h
Vandepitte *et al.*[38]	Liposomal ($n=26$) Control ($n=24$)	Major shoulder surgery	Interscalene brachial plexus block, US	General anaesthesia	2 : 1 Liposomal bupivacaine and bupivacaine 0.25%, 15 ml	Bupivacaine 0.25%, 15 ml	Acetaminophen, NSAID, dexamethasone, tramadol	3 units in rest pain score (time interval not specified)
Vandepitte *et al.*[39]	Liposomal ($n=16$) Control ($n=16$)	Dupuytren contracture release	Median and ulnar nerve blocks at the forearm, US	Not specified	2 : 1 Liposomal bupivacaine and bupivacaine 0.5%, 7.5 ml	Bupivacaine 0.5%, 7.5 ml	Acetaminophen, NSAID, tramadol	Not specified
Weksler *et al.*[40]	Liposomal ($n=25$) Control ($n=25$)	Video-assisted thoracic surgery	Port site infiltration and intercostal nerve block, direct visualisation by surgeon	General anaesthesia	Liposomal bupivacaine, 10 ml	Bupivacaine with epinephrine 5 μg ml^{-1}, 10 ml, concentration not specified	Acetaminophen, NSAID, oxycodone, PCA of morphine or hydromorphone	25% in opioid consumption during hospital length of stay
Wong *et al.*[41]	Liposomal ($n=75$) Control ($n=73$)	Bariatric surgery	TAP block, direct visualisation by surgeon	General anaesthesia	2 : 3:10 Liposomal bupivacaine, bupivacaine 0.25% and normal saline,150 ml	1 : 2 Bupivacaine 0.25% with normal saline, 150 ml	Acetaminophen, NSAID, morphine, PCA of fentanyl	Not specified
Xie *et al.*[42]	Liposomal ($n=40$) Control ($n=47$)	Penile prothesis	Dorsale penile and penile ring block, landmark	General anaesthesia	2 : 1 Liposomal bupivacaine and normal saline, 30 ml	Ropivacaine 0.5%, 30 ml	Acetaminophen, oxycodone, morphine	Not specified
Yeap *et al.*[43]	Liposomal ($n=38$) Control ($n=40$)	Colorectal surgery	Quadratus lumborum block, US	General anaesthesia	1 : 2 Liposomal bupivacaine and bupivacaine 0.125%, 60 ml, with dexamethasone 4 mg	Bupivacaine 0.25%, 60 ml, with dexamethasone 4 mg	Acetaminophen, gabapentin, oxycodone, hydromorphone	60% in opioid consumption (time interval not specified)
Zhang *et al.*[44]	Liposomal ($n=43$) Control ($n=43$)	Unilateral mastectomy	Interpectoral plane block, US	General anaesthesia	2 : 3 Liposomal bupivacaine, and normal saline, 50 ml	Bupivacaine 0.5%, 30 ml	Not specified	Not specified

Iv, intravenous; PCA, patient-controlled analgesia; TAP, transversus abdominis plane; US, ultrasound.

Fig. 2 Cochrane collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias.

Discussion

This systematic review and meta-analysis with trial sequential analysis explored the analgesic efficacy of liposomal bupivacaine for peripheral nerve blocks when compared with any long-acting local anaesthetics. On the basis of the analysis of 27 randomised controlled trials representing a total of 2122 patients, we established that liposomal bupivacaine statistically decreased pain scores at rest at 24, 48 and 72 postoperative hours, but without an impact on interval morphine consumption or postoperative nausea and vomiting. The significant difference in the presence of nausea or vomiting at 72 postoperative hours is based on six trials and 314 patients and might represent a type I error in the setting of an equivalent opioid consumption between groups. Our subgroup analysis according to the type of block revealed that there is no significant difference in pains scores at rest when liposomal bupivacaine is compared with long-acting local anaesthetics for field blocks. Firm evidence is reached according to the trial sequential analysis and the quality of evidence is moderate for all outcomes following the GRADE assessment system.

Some discussion of the small mean difference in pain scores at rest (< one unit) between groups at 24, 48 and 72 postoperative hours is required. Twenty years ago, the question of what represents a minimal clinically important difference in pain scores was investigated.[45,46] After examining 2724 patients, Farrar *et al.*[45] concluded that a reduction of 30% or two points on an 11-unit pain score scale represents a clinically important difference among patients suffering from medical conditions, while Cepeda *et al.*[46] stated that a difference of 1.3 units or a 20% reduction is clinically relevant after investigating 700 patients who underwent all types of surgery. More recently, after enrolling 224 patients undergoing different types of surgery, Myles *et al.*[47] determined that a one-unit difference in pain score is a relevant improvement in contemporary practice. In this meta-analysis, the mean difference between groups is consistently less than one unit up to postoperative hour 72 and thus does not reach the threshold of clinical relevance: and there was no reduction in opioid consumption. These facts question the administration of liposomal bupivacaine in the clinical practice, especially in light of the high cost of the medication: liposomal bupivacaine is 100 times more expensive than bupivacaine.[48]

Of note, among the different peripheral nerve blocks, liposomal bupivacaine is approved in adults for the interscalene brachial plexus block by the United States Food and Drug Administration,[6] and for brachial plexus, femoral nerve and field blocks by the European Medicines Agency,[7] which means that administration of liposomal bupivacaine for other peripheral nerve blocks represent an off-label route of administration. This raises questions

Fig. 3 Rest pain score at 24 postoperative hours in patients receiving liposomal bupivacaine or long-acting local anaesthetics (bupivacaine, ropivacaine) analysed according to peripheral nerve versus field blocks. LA, local anaesthetics.

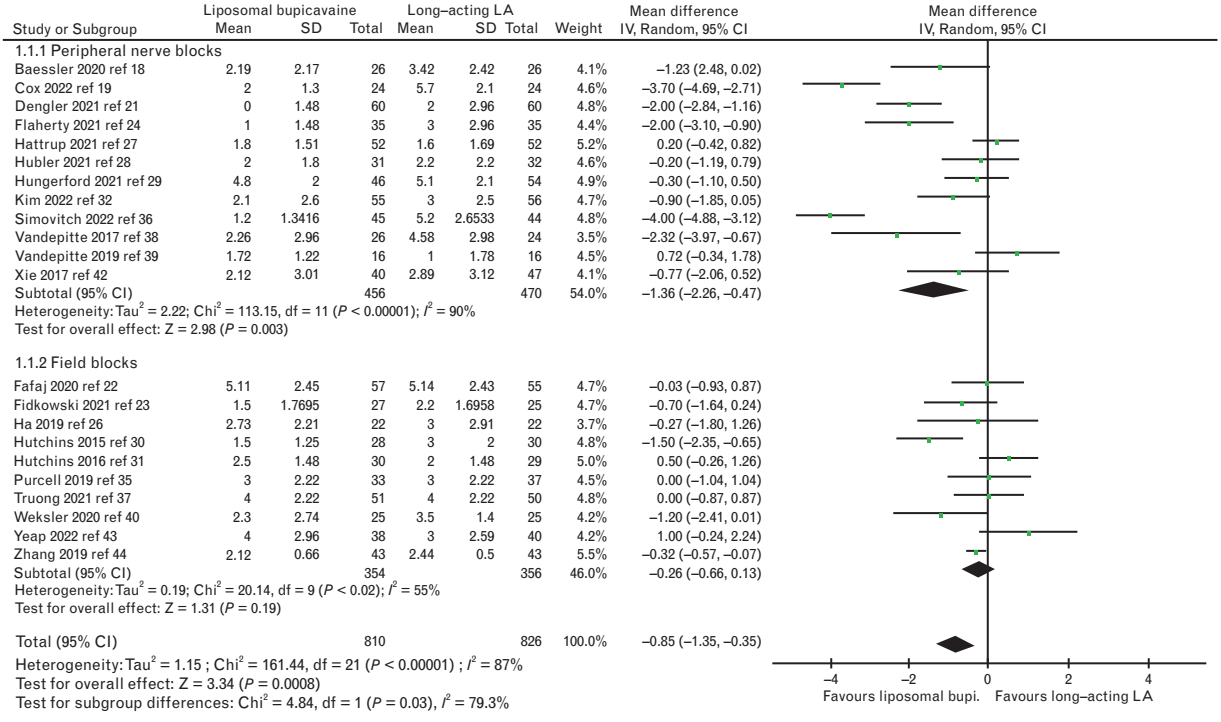

Table 2 **Secondary pain-related outcomes**

Outcome	Number of trials	References	Total number of patients		Mean difference [95% CI] or relative risk [95%CI]	I^2 (%)	*P* value for overall effect
			Liposomal Bupivacaine	Long-acting local anaesthetics			
Rest pain score at 2 postoperative hours (analogue scale 0 to 10)	15	Baessler *et al.*,[18] Cox *et al.*, Fafaj *et al.*,[22] Flaherty *et al.*,[24] Ha *et al.*,[26] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Kim *et al.*,[32] Purcell *et al.*,[35] Simovitch *et al.*,[36] Truong *et al.*,[37] Weksler *et al.*,[40] Xie *et al.*,[42] Yeap *et al.*,[43] Zhang *et al.*[44]	552	563	-0.3 [-0.7 to 0.1]	70	0.19
Rest pain score at 48 postoperative hours; analogue scale 0 to 10	24	Baessler *et al.*,[18] Cox *et al.*,[19] Dengler *et al.*,[21] Fafaj *et al.*,[22] Fidkowski *et al.*,[23] Flaherty *et al.*,[24] Ha *et al.*,[26] Hattrup *et al.*,[27] Hubler *et al.*,[28] Hungerford *et al.*,[29] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Kim *et al.*,[32] Purcell *et al.*,[35] Simovitch *et al.*,[36] Truong *et al.*,[37] Vandepitte *et al.*,[38] [30]Vandepitte *et al.*,[39] Weksler *et al.*,[40] Wong *et al.*,[41] Xie *et al.*,[42] Yeap *et al.*,[43] Zhang *et al.*[44]	871	888	-0.7 [-1.1 to -0.3]	82	0.001
Rest pain score at 72 postoperative hours; analogue scale 0 to 10	21	Baessler *et al.*,[18] Cox 2022,[19] Dengler 2021,[21] Fafaj 2020,[22] Fidkowski 2021,[23] Flaherty 2021,[24] Ha 2019,[26] Hattrup 2021,[27] Hubler 2021,[28] Hungerford 2021,[29] Hutchins 2015,[30] Hutchins 2016[31], Kim 2022,[32] Purcell 2019,[35] Simovitch 2022,[36] Truong 2021,[37] Vandepitte 2017,[38] Vandepitte 2019,[39] Xie 2017,[42] Yeap 2022,[43] Zhang 2019[44]	775	795	-0.7 [-1.1 to -0.3]	80	<0.001

Table 2 (*continued*)

Outcome	Number of trials	References	Total number of patients		Mean difference [95% CI] or relative risk [95%CI]	I^2 (%)	*P* value for overall effect
			Liposomal Bupivacaine	Long-acting local anaesthetics			
Interval iv morphine consumption at 0 to 24 postoperative hours (mg)	17	Baessler *et al.*,[18] Dawes *et al.*,[20] Dengler *et al.*,[21] Fafaj *et al.*,[22] Fidkowski *et al.*,[23] Flaherty *et al.*,[24] Hubler *et al.*,[28] Hungerford *et al.*,[29] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Kim *et al.*,[32] Purcell *et al.*,[35] Simovitch *et al.*, Truong *et al.*,[37] Vandepitte *et al.*,[38] Weksler *et al.*,[40] Xie *et al.*[42], Yeap *et al.*[43]	694	720	-2.5 [-5.8 to 0.9]	97	0.13
Interval iv morphine consumption at 24 to 48 postoperative hours (mg)	14	Dawes *et al.*,[20] Fafaj *et al.*,[22] Fidkowski *et al.*,[23] Flaherty *et al.*,[24] Hubler *et al.*,[28] Hungerford *et al.*,[29] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Kim *et al.*,[32] Purcell *et al.*,[35] Simovitch *et al.*, Truong *et al.*,[37] Vandepitte *et al.*,[38] Weksler *et al.*,[40] Yeap *et al.*[43]	570	583	-2.4 [-5.9 to 0.8]	95	0.14
Interval iv morphine consumption at 48 to 72 postoperative hours (mg)	13	Baessler *et al.*,[18] Fafaj *et al.*,[22] Fidkowski *et al.*,[23] Flaherty *et al.*,[24] Hubler *et al.*,[28] Hungerford *et al.*,[29] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Kim *et al.*,[32] Purcell *et al.*,[35] Simovitch *et al.*, Truong *et al.*,[37] Vandepitte *et al.*[38], Yeap *et al.*[43]	528	539	-1.7 [-3.6 to 0.2]	86	0.06
Presence of nausea or vomiting at 24 postoperative hours	2	Hubler *et al.*[28], Yeap *et al.*[43]	69	72	1.1 [0.5 to 2.1][a]	0	0.86
Presence of nausea or vomiting at 48 postoperative hours	2	Hubler *et al.*[28], Yeap *et al.*[43]	69	72	0.9 [0.4 to 2.0][a]	12	0.81
Presence of nausea or vomiting at 72 postoperative hours	6	Hubler *et al.*,[28] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Motafek *et al.*,[34] Vandepitte *et al.*[39], Yeap *et al.*[43]	155	159	0.6 [0.3 to 0.9][a]	29	0.02
Hospital length of stay (h)	16	Dawes *et al.*,[20] Dengler *et al.*,[21] Fafaj *et al.*,[22] Fidkowski *et al.*,[23] Guerra *et al.*,[25] Ha *et al.*,[26] Hattrup *et al.*,[27] Hubler *et al.*, Hungerford *et al.*,[29] Hutchins *et al.*,[30] Hutchins *et al.*,[31] Purcell *et al.*,[35] Truong *et al.*,[37] Weksler *et al.*,[40] Wong *et al.*,[41] Zhang *et al.*	686	695	-0.6 [-1.4 to 0.3]	48	0.20

CI, confidence interval; iv, intravenous. [a]These are relative risk (95% confidence interval).

about the use of liposomal bupivacaine for brachial plexus blocks, as the neural structures of this plexus are more prone to injury secondary to its elevated ratio of neural/connective tissue when compared with more distal nerves.[49] Despite our willingness to report the incidence of nerve injury, we were unable to draw any conclusion since this outcome was not sought by the included trials.

This meta-analysis contains several weaknesses. First, we were confronted with an elevated heterogeneity coefficient in our primary outcome that we could not explain with our hypotheses and different subgroup analyses. Indeed, differences in the types of blocks, doses of liposomal bupivacaine administered, adjuncts used, nerve block technique, types of local anaesthetics, anaesthetic strategy or prescription of baseline analgesia were parameters that only partially reduced the heterogeneity. Other factors might impact this heterogeneity such as the spread of the local anaesthetics, which is difficult to statistically assess, especially when it is not described in the different articles. Second, we included seven trials[18,32,34,36,37,40,43] that combined long-acting local anaesthetic with a perineural adjunct such as epinephrine or dexamethasone; however, as the analgesic duration of such a combination would last maximum 24 h, we do not believe it reduces the impact of our findings. Finally, none of the trials compared liposomal bupivacaine with levobupivacaine; however, it is doubtful that results would differ from current comparators such as bupivacaine or ropivacaine.

To conclude, there is moderate level evidence that liposomal bupivacaine reduces rest pain scores by 0.9 out of 10 units, when compared with long-acting local anaesthetics at 24 hours after surgery, and by 0.7 up to 72 hours after surgery.

Table 3 Quality of evidence assessment for each outcome

Quality assessment						Summary of findings		
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of participants	Conclusion	Quality of evidence (GRADE)
Rest pain score at 2 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1115	No difference between groups	Moderate quality (⊕⊕⊕O)[e]
Rest pain score at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1636	Reduced rest pain score in liposomal bupivacaine group	Moderate quality (⊕⊕⊕O)[e]
Rest pain score at 48 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1759	Reduced rest pain score in liposomal bupivacaine group	Moderate quality (⊕⊕⊕O)[e]
Rest pain score at 72 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1570	Reduced rest pain score in liposomal bupivacaine group	Moderate quality (⊕⊕⊕O)[e]
Interval iv morphine equivalent consumption at 0–24 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1414	No difference between groups	Moderate quality (⊕⊕⊕O)[e]
Interval iv morphine equivalent consumption at 24–48 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1153	No difference between groups	Moderate quality (⊕⊕⊕O)[e]
Interval iv morphine equivalent consumption at 48–72 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1067	No difference between groups	Moderate quality (⊕⊕⊕O)[e]
Presence of nausea or vomiting at 24 postoperative hours	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	141	No difference between groups	Moderate quality (⊕⊕⊕O)[f]
Presence of nausea or vomiting at 48 postoperative hours	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	141	No difference between groups	Moderate quality (⊕⊕⊕O)[f]
Presence of nausea or vomiting at 72 postoperative hours	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	314	Presence of nausea or vomiting reduced in liposomal bupivacaine group	Moderate quality (⊕⊕⊕O)[f]
Hospital length of stay (hours)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	1381	No difference between groups	Moderate quality (⊕⊕⊕O)[e]

[a] As only a limited number of studies suffered from a high-risk of bias, we estimated there is no major limitation. [b] I^2 above 50%. [c] Consistent definition of the reported outcome. [d] No serious imprecision as the clinical decision would not be modified whether the upper of lower boundary limit of the confidence interval represented the truth. [e] We rated down the quality of evidence for serious inconsistency. [f] We rated down for limitations, as six trials or less reported this outcome.

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