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Liposomal bupivacaine and postoperative opioid consumption for oncologic and non-oncologic breast procedures: a literature review and meta-analysis

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Abstract

Reduction of postoperative analgesic consumption in breast cancer patients is of significant clinical interest. Some studies have demonstrated promising results related to the efficacy of liposomal bupivacaine (LB), a long-acting local analgesic used intraoperatively, in reducing opioid consumption after aesthetic breast surgery. The purpose of this review is to evaluate postoperative opioid consumption when using LB in aesthetic breast surgery vs oncologic breast surgery to help clinicians better understand trends in pain outcomes in breast cancer patients. A literature search was conducted to identify records reporting postoperative opioid consumption for patients undergoing oncologic mastectomy with and without breast reconstruction (BR) and aesthetic breast surgery. Of the 779 records reviewed, 15 met inclusion criteria representing 2,453 patients. Of these, none of the oncologic procedures without BR showed reduced opioid consumption with LB. A meta-analysis of oncologic procedures with BR and aesthetic breast procedures showed significant effect size (ES) estimates of reduced postoperative opioid

consumption when using LB compared to control anesthetics [ES: 1.698 ± 0.8624; 95% confidence interval (CI): 0.005, –3.390; p = 0.049 and ES: 1.212 ± 0.3053; 95% CI: 1.810–0.613; p < 0.001, respectively). In conclusion, intraoperative LB reduces postoperative opioid consumption for oncologic breast surgery with BR and aesthetic breast procedures. LB is understudied in mastectomy without BR and more research is needed. Neoadjuvant treatment and procedural differences could contribute to different pain outcomes. Further investigation could help uncover the etiology of post mastectomy pain syndromes.

Key words: breast cancer; liposomal bupivacaine; breast surgery; mastectomy; postoperative pain; long-acting analgesics; opioid consumption

Introduction

Treatment of postoperative pain and the appropriate administration of opioid analgesics is an ongoing clinical challenge for many surgical procedures including breast surgery. Breast cancer is the most frequently diagnosed type of cancer among women in the United States, and over 100,000 mastectomies are performed every year [1]. An increasing proportion of these mastectomies are performed with immediate reconstruction or oncoplastic techniques, and over 300,000 breast surgeries are performed each year for both cosmetic and oncological purposes [2].

Postoperative pain from breast procedures was previously considered a minor consequence, but recent attention has been brought to adverse sequelae of inadequately treated postoperative pain for breast procedures, including post mastectomy persistent pain syndrome (PMPS), a subset of post-breast surgery pain syndrome (PBSPS) which can persist for years [3–5]. The etiology of PMPS/PBSPS is hypothesized to be related to the placement of the intercostobrachial nerve through the axilla, putting it at risk for traction injury during axillary lymph node dissection, breast reconstruction, breast reduction, and total mastectomy [6]. While awareness of this risk is an important aspect of surgical planning, traction injuries can be unavoidable and difficult to detect, and this likely contributes to the wide range of postoperative symptoms seen clinically. Postoperative pain is a known risk factor for the development of PBSPS [7], and reducing postoperative pain for breast cancer surgery has been shown to achieve a more rapid return to baseline and reduce health care costs by shortening length of hospital stay [8].

Traditionally, breast surgery postoperative pain has been treated with opioids and nonsteroidal anti-inflammatory drugs, but many of these drugs have adverse effects including nausea, severe constipation, and dyspepsia [9]. Additionally, the use of opioids as a primary treatment modality is associated with many adverse effects due to the high potential for misuse. The U.S. Department of Health and Human Services declared the opioid epidemic a public health emergency in 2017 [10], and approximately 500,000 people have died of opioid related overdoses in the United States according to the Centers for Disease Control and Prevention (CDC) [11]. Subsequently, there has been increased emphasis placed on multimodal pain control to decrease administration of postoperative analgesics, including long-acting local anesthetics that can be used intraoperatively to reduce postoperative pain and avoid unwanted side effects.

Liposomal bupivacaine (LB), also known as Exparel, is a long-acting form of bupivacaine that was approved by the Food and Drug Administration (FDA) in 2011. The LB formula approved in the United States is a DepoFoam formulation, which is a multivesicular liposome technology with particle suspension in an isotonic aqueous solution. This consists of individual water-filled chambers dispersed through a lipid matrix, giving LB its long-acting effects. Hence, the anesthetic was approved for prolonged postoperative pain control, with effects lasting up to 72 hours [12]. In 2015, the FDA expanded approval of LB for local infiltration in thoracic, orthopedic, abdominal, and some breast procedures. Subsequent investigations into off label use for peripheral and intercostal nerve blocks and epidural use followed soon after [13]. Thus, there is significant interest in determining if LB can help reduce postoperative pain and analgesic consumption in breast surgeries.

State of the Art

Bupivacaine with and without liposomal formulation is publicized as an excellent choice for local anesthesia for breast surgery due to its ability to be installed into the dissection space and comparatively long half-life of 4.8 hours even without liposomal formulation [14]. Nonetheless, the full efficacy and safety profile of LB for individual breast procedures, including mastectomies, mammoplasties, breast augmentation/reduction, and lumpectomies, has not yet been fully established. Results in the literature so far have been contradictory, and a recent review comparing postoperative analgesic consumption in oral morphine equivalents (OMEs) of

LB to ropivacaine in randomized control trials of all surgical procedures showed no consistent benefit associated with LB [15]. Another systematic review of LB in plastic surgery procedures including breast reconstruction, augmentation mammaplasty, and abdominoplasty demonstrated equivalent or more effective pain control compared to traditional anesthetics. To the authors' knowledge, no similar analysis exists specifically to evaluate LB efficacy in oncologic breast procedures.

The purpose of this review is to evaluate the literature available on the efficacy of LB in decreasing postoperative opioid consumption when compared to other common analgesic options in patients undergoing both aesthetic breast surgery and oncologic breast surgery with and without BR.

Materials and methods

A search was conducted of PubMed, Embase, Cochrane, and WebofScience from inception to November 5th, 2022, to identify cohort, prospective, retrospective, control, and/or clinical trials describing postoperative outcomes of breast surgeries. Inclusion criteria were: 1) patients had aesthetic or oncologic breast surgery; 2) there was an LB study arm and an alternative anesthetic study arm; and 3) postoperative opioid consumption in oral morphine equivalents (OMEs) was included as an outcome. Exclusion criteria were: 1) technique articles, editorials, case reports, animal studies, 2) no analysis of outcomes (descriptive statistics only). Keywords were used including "liposomal bupivacaine" "Exparel" "mastectomy" "opioid" "postoperative pain" "breast" "breast surgery" and all relevant synonyms determined using MeSH (Medical Subject Headings) terms.

Abstracts and articles were examined and screened independently by two reviewers with a third for arbitration. No automation tools were used in the analysis process. Initially, abstracts and titles were screened to retain only studies of breast surgeries which included LB as a method of intraoperative pain control. Then, the full text of those articles was retrieved and reviewed to identify studies that included a control anesthetic arm and reported postoperative opioid consumption.

Relevant data was extracted from the studies including sample size, mean, standard deviation, and effect sizes were calculated. A meta-analysis was performed using SPSS v28. Forest Plots

were generated using GraphPad Prism 9.2.0. Effect size was measured with Cohen's d with continuous outcome and random effect weights including within and between study variance [16]. Postoperative opioid consumption that was not already reported as OME was converted using the CDC opioid guidelines [17]. Some studies included both OME per hour throughout the recovery time and total OME. Only total postoperative OME was included in the meta-analysis.

Results

Characteristics of included studies

Out of the 779 nonduplicate records reviewed, 15 met inclusion criteria representing 2,453 patients total (1,513 in the LB arm and 940 in control anesthetic arms) (Supplementary File — Figure S1: PRISMA flow diagram [18]). The control anesthetic used was a formulation of non-liposomal bupivacaine for 10 of the studies (67%), an unreported historical control anesthetic for one study (6.7%), intraoperative ketorolac for one study (6.7%), and ropivacaine or cocktail including ropivacaine for three of the studies (20%). Risk of bias in included studies was low or with minor concerns only, including selection of patients from a specific group, poor reporting of detection methods, and lack of detail included in the outcomes that are reported (Supplementary File — Table S1).

Of the non-oncologic breast surgery procedures or delayed reconstruction only, there were 282 cases of submuscular augmentation mammaplasty (35.8%), 391 cases of delayed reconstruction with abdominally based flap (49.7%), and 113 cases of reduction mammoplasty (14.4%). Of the oncologic breast surgery with BR, all were total mastectomy (uni- and bilateral, with or without lymph node dissection), and 97 were immediate reconstruction with tissue expander (15.3%), 90 were implant based (14.2%), and 447 were with microsurgical autologous reconstruction (70.5%).

Narrative results

We identified a total of seven articles that met inclusion criteria that described outcomes of LB used in aesthetic breast surgeries, including augmentation, mammaplasty, mastopexy, and reduction. Six of these studies demonstrated statistically significant benefits in reduced oral morphine equivalents (OMEs), patient reported VAS pain scores, and reduced hospital stay in LB

groups compared to alternative anesthetic agents [19–21, 22–28]. Only one study demonstrated no difference in outcomes of LB compared to alternative anesthetic [29] (Tab. 1).

We identified six additional studies that studied outcomes of LB used in the context of oncologic mastectomy with immediate plastic surgery BR. All of these showed quantitative benefit of LB compared to another anesthetic agent, including decreased mean length of hospital stay, lower VAS pain score, and reduced postoperative opioid consumption [19, 30–33]. One review demonstrated that enhanced recovery after surgery (ERAS) principles in conjunction with LB intraoperatively could make outpatient mastectomies with submuscular impact/tissue expander and direct-to-implant reconstruction feasible in the outpatient setting [30] (Tab. 2).

We identified only two articles evaluating the postoperative outcomes of LB with mastectomy alone without any reconstruction or plastic surgery procedures [34, 35]. This demonstrated no consistent benefit of LB over any other specific local anesthetic agent (Tab. 3).

Table 1. Summary of individual studies included in the review presented in the following order: aesthetic only, oncologic procedures with reconstruction, and oncologic mastectomy without reconstruction

Meta analysis of postoperative opioid consumption

We performed a meta-analysis of all non-oncologic procedures including delayed reconstruction (> 1 year) using Cohen's d effect size. Meta analysis showed overall decreased postoperative opioid consumption with the use of LB for these cases, with an effect size of –1.212 ± 0.3053 with significance of $p < 0.001$ (95% CI: 0.613–1.81) (Fig. 1). Meta analysis of continuous outcomes using Cohen's d effect size measurement of studies including immediate reconstruction after oncologic breast surgery showed decreased postoperative opioid consumption with overall effect size of –1.698 ± 0.8624 effect size of using LB compared to other control anesthetics (95% CI: 0.005, –3.390; $p = 0.049$) (Fig. 2). Meta analysis of continuous outcomes using Cohen's d effect size measure demonstrated a nonsignificant positive effect size of use of LB compared to control anesthetics for mastectomy without reconstruction (ES: 0.185 ± 0.0986; 95% CI: –0.008–0.378; $p = 0.061$) (Fig. 3).

Figure 1. A. Forest Plot of aesthetic breast surgery, overall effect size -1.212 (*95% CI 1.810, -0.613; p<0.001*) **B)** Forest Plot of oncoplastic breast surgery with BR (autologous and implant based), overall effect size -1.698 (95% CI –3.390,–0.378; *p=0.049*) **C)** Forest Plot of oncoplastic breast surgery without reconstruction, overall effect size 0.185 (95% CI -0.008,0.378; *p=0.61*). *Negative effect size is correlated with decreased postoperative opioid consumption.*

Discussion

The most relevant findings of the current study were that intraoperative use of LB resulted in decreased postoperative opioid consumption when compared to control anesthetics in oncologic breast surgery with immediate BR as well as aesthetic breast surgery. The same trend was not seen for the use of intraoperative LB for oncologic breast surgery without BR, and a much smaller volume of information was available for oncologic breast surgery without BR.

Our results indicate a trend towards plastic surgery breast procedures having significant improvement in pain management with the use of LB compared to other anesthetics. Similar benefits have been shown for other plastic surgery procedures, including microvascular reconstruction and abdominoplasty [36, 37]. To the authors' knowledge, no meta-analysis exists with quantitative outcomes based on postoperative analgesic consumption for breast cancer related surgeries with and without immediate BR and comparison to pain outcomes cosmetic breast surgery procedures. Given that PMPS and PBSPS from all breast surgery procedures are hypothesized to have the same etiology, comparing the pain outcomes of long-acting analgesics like LB in different types of breast cancer procedures may shed light on the causes of these syndromes.

The benefits of LB in breast cancer procedures without immediate BR are not conclusively demonstrated in the literature. There are certain characteristics of aesthetic breast procedures and oncologic breast procedures without any reconstruction that may contribute to a difference in the efficacy of LB. Many reconstructions are performed using a flap inset, which lends itself to the use of a local anesthetic infiltration, compared to total mastectomy where there is less fat/breast tissue left for infiltration of LB. Thus, it is of significant clinical interest to determine if the

postoperative pain outcomes vary significantly for patients undergoing mastectomy with immediate BR compared to without and what procedures are the most appropriate for the use of LB. This will inform physicians in the management of postoperative pain for patients undergoing breast cancer procedures with and without reconstruction with the goal of reducing incidence of PMPS/PBSPS and opioid consumption.

Non-opioid pain management control has been demonstrated to improve the quality of life of patients suffering from cancer-related pain [38]. In the intraoperative setting, alternatives to general anesthesia, such as paravertebral blocks, have been shown to be cost-effective in controlling post-mastectomy pain in cancer patients [39]. However, its use may be limited to centers with interventional pain specialists. In the acute setting, non-opioid pain control methods have been shown to not only alleviate physical discomfort but also provide significant psychological benefits and sense of wellbeing [40, 41]. These factors are important for patients recovering from surgery while already dealing with emotionally charged life-changing stress related to their cancer diagnosis and expected physical changes occurring from surgery. Another level of complexity is added when considering adjuvant/neoadjuvant treatments that contribute to postoperative pain. The utility of LB should be further studied in the context of pain from these treatments.

LB is only available at significantly increased cost compared to ropivacaine or the non-liposomal formulations of LB. Exparel, the primary manufacturer of LB in the United States, prices their formulations as 198.84 USD per 133 mg dose and 354.53 USD per 266 mg dose, which represents approximately 15x the cost of equivalent dosage ropivacaine and 40x the cost of equivalent dose non-liposomal bupivacaine [42–44]. For this reason, conclusive evidence of definitive benefits is necessary prior to widespread use, the cost of which would be passed on to hospitals and patients. Additionally, bupivacaine has been shown to have cardiotoxic and central nervous side effects when compared to alternative local anesthetics [45, 46]. If LB truly reduces postoperative pain and opioid consumption, then this increased cost for an intraoperative analgesic coupled with possible adverse effects would be justifiable. However, conclusive evidence is still needed to determine the benefits of LB for oncologic procedures.

Limitations

This study has several limitations, primarily stemming from the nature of systematic reviews. The review is limited to current available literature and completed studies. The authors recognize that both publication bias and selective outcome reporting make it more challenging to draw conclusions about the utility of LB compared to other analgesic options. Further, the heterogeneity displayed from the meta-analysis results make it difficult to draw any strong conclusions from the synthesized data. Additionally, several risks of bias were identified in several studies. However, these risks were low in most studies and overall risk was mitigated by including only studies with a control anesthetic arm and inclusion of statistical results, thereby limiting the inclusion of studies without rigorous study design.

Future directions

More studies need to be done on outcomes of LB for oncological procedures to definitively determine if there are any clinical or economic benefits. We hope that emphasis on control of postoperative pain in breast procedures can help reduce the occurrence of PMPS/PBSPS and increase our understanding of causes and risk factors.

Conclusion

More literature is available on outcomes of intraoperative LB in aesthetic breast surgeries than purely oncological breast surgeries. The studies that have been done show a trend towards decreased postoperative opioid consumption and better pain control in plastic surgery procedures and mastectomies with BR when LB is used, but no conclusive trends exist for breast cancer surgeries without reconstruction. There are many benefits of using intraoperative long-acting pain control over postoperative analgesic agents, but newer formulations, like LB, are available at a premium cost, and thus evidence of their benefit needs to be obtained before incurring this cost on patients, hospitals, and the public. Given the negative long term adverse outcomes of inadequately treated postoperative pain for breast procedures and the current opioid crisis, we are hopeful that intraoperative analgesic agents can provide a useful alternative. It remains to be determined if the benefits of LB seen in plastic surgery breast operations can be extended to oncological procedures without any reconstruction.

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Figure 1. A. Forest Plot of aesthetic breast surgery, overall effect size –1.212 (95% CI: 1.810, –0.613; $p < 0.001$); negative effect size is correlated with decreased postoperative opioid consumption. **B.** Forest Plot of oncoplastic breast surgery with BR (autologous and implant based), overall effect size –1.698 (95% CI: –3.390,–0.378; p=0.049); negative effect size is correlated with decreased postoperative opioid consumption. C) Forest Plot of oncoplastic breast surgery without reconstruction, overall effect size 0.185 (95% CI: –0.008–0.378; p = 0.61); negative effect size is correlated with decreased postoperative opioid consumption

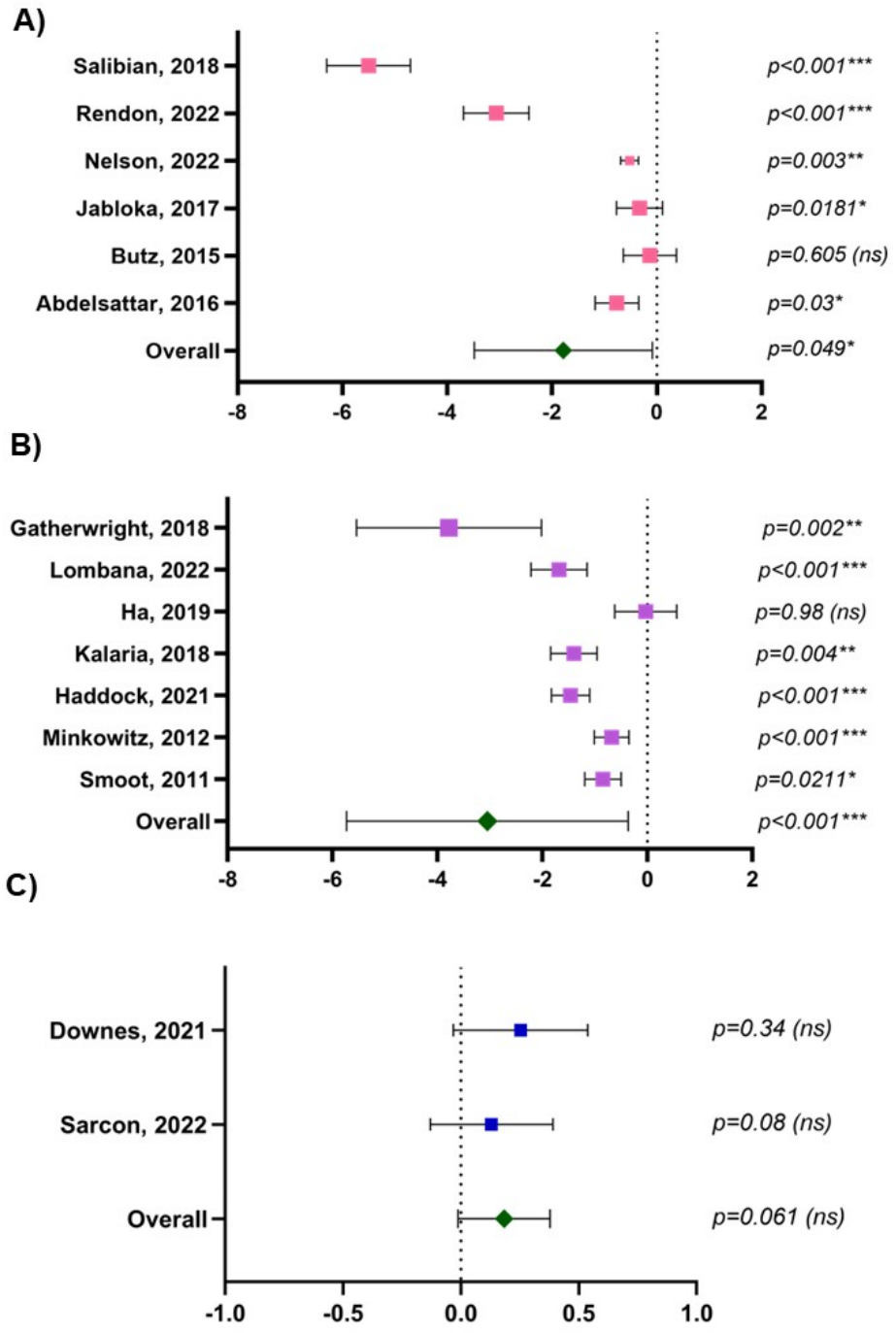

A)
Salibian, 2018
Rendon, 2022
Nelson, 2022
Jabloka, 2017
Butz, 2015
Abdelsattar, 2016
Overall
p<0.001***
p<0.001***
p=0.003**
p=0.0181*
p=0.605 (ns)
p=0.03*
p=0.049*
-8
-6
-4
-2
0
2
B)
Gatherwright, 2018
Lombana, 2022
Ha, 2019
Kalaria, 2018
Haddock, 2021
Minkowitz, 2012
Smoot, 2011
Overall
p=0.002**
p<0.001***
p=0.98 (ns)
p=0.004**
p<0.001***
p<0.001***
p=0.0211*
p<0.001***
-8
-6
-4
-2
0
2
C)
Downes, 2021
Sarcon, 2022
Overall
p=0.34 (ns)
p=0.08 (ns)
p=0.061 (ns)
-1.0
-0.5
0.0
0.5
1.0

Table 1. Summary of individual studies included in the review presented in the following order: aesthetic only, oncologic procedures with reconstruction, and oncologic mastectomy without reconstruction

Study	**Article type**	**Operation / Reconstruction**	**Control Anesthetic (CA)**	**n_{total} n_{LB} (%) n_{CA} (%)**	**Anesthetic dosage**	**Outcomes**	
						As reported	**Oral Morphine Eq (OME)**
Aesthetic Breast Procedures							
Smoot et al., 2011 (Aesthet Surg J)	Clinical Trial	Submuscular augmentation mammaplasty	HCl Bupivacaine	n_{total} = 136 n_{LB} = 66 (49) n_{CA} = 70 (51)	LB 600 mg B HCl 200 mg	Total opioid consumption lower in LB at 24h (p = 0.0211) 48 h (p = 0.0459) Mean pain score showed no significant difference (441.5 LB *vs.* 468.2 B H Cl, p = 0.3999)	**LB:** 13.5 OME total postop **Control:** 30.4 OME p = 0.0579
Minkowitz et al., 2012 (Aesthet	Randomized, double-blind control trial	Bilateral, cosmetic, sub-	Bupivacaine HCl	n_{total} = 146	LB 532 mg	Pain intensity at rest and	**LB:** 22.3 OME

Surg J)		muscular breast augmentation		n_{LB} = 73 (50) n_{CA} = 73 (50)	B HCl 200 mg	with opioid use demonstrated statistically significant advantages at multiple time points up to and including 60 hours No difference in patients reporting breast pain (9.7 *vs.* 9.4%)	total postup up to 60 hours **Control:** 29.1 OME total postop up to 60 hours $p \leq 0.0006$
Haddock et al., 2021 (PRS)	Retrospective review	Delayed DIEP flap reconstruction	Historical control anesthetic (CA) or ERAS pathway	n_{total} = 216 n_{LB} = 80 (37) n_{ERAS} = 69 (32)	NR	Decrease in LOS (length of stay) in LB group (mean ± SD 2.550 ± 0.840 *vs.* 3.217± 0.802 vs. 3.642 ± 0.829 days, $p < 0.001$) Decreased opioid	**LB:** 115.5 ± 54.6 OME total postop **Control:** ERAS 146.8 ± 93.9 OME total postop CA 275.7 ±

				n_{CA} = 67 (31)		consumption in LB group (mean ± SD 115.5 ± 54.6 *vs.* 146.8 ± 93.9 *vs.* 275.7 ± 151.1 OME, p < 0.001)	151.1 OME total postop p < 0.001
Kalaria et al., 2018 (Ann Plast Surg)	Retrospective review	Reduction mammaplasty	Bupivacaine with epinephrine	n_{total} = 113 n_{LB} = 79 (70) n_{CA} = 34 (30)	LB 266 mg B 150 mg with 1:200,000 epinephrine	Decrease in pain score at discharge for Obese Class I with LB (mean difference 2.44, p = 0.018) Decrease in opioid consumption for patients in Obese class III Mean difference 7.175, p = 0.004)	Mean difference 7.175 total OME postop LB *vs.* bupivacaine, p = 0.004
Ha et al., 2019	Randomized, single-blind	Abdominally Based	Bupivacaine with	n_{total} = 44	LB	No difference	**LB:** 283 (90–

(PRS)	control trial	Autologous Microvascular Breast Reconstruction (majority delayed)	epinephrine	n_{LB} = 22 (50) n_{CA} = 22 (50)	266 mg B 75 mg with 1:200,000 epinephrine	in time to oral narcotics (median 15.5 *vs.* 18.2 hours, p = 0.45) No difference in total opioid use (median 283 *vs*. 300 OME p = 0.98) No difference in duration of admission (median 2.91 *vs.* 3.56 days, p = 0.20)	765) total OME postop **Control:** 300 (108–684) total OME postop p = 0.98
Lombana et al., 2022 (PRS)	Retrospective review	Abdominally Based Autologous Microvascular Breast Reconstruction	Local anesthetic cocktail of bupivacaine with epinephrine (LAC) or control anesthetic (CA) before	n_{total} = 104 n_{LB} = 38 (36)	LB 266 mg LAC 60 cc of 0.25% plain bupivacaine with 1:200,000	Increase in maximum POD 1 pain score in LB group (7.1 *vs.* 5.7 *vs.* 6.5, p = 0.02)	**LB:** 240 ± 157 total OME postop **Control:**

		(majority delayed)	ERAS and TAP block	n_{LAC} = 30 (29) n_{CA} = 36 (35)	epinephrine, 30 mg of ketorolac, 50 µg of dexmedetomidine CA NR	Decrease in total opioid consumption in LB and LAC groups (mean ± SD 240 ± 157 *vs.* 135 ± 159 *vs.* 633 ± 293 OME, p < 0.0001) No difference in LOS (mean ± SD 4.1 ± 1.2 *vs.* 4.2 ± 1.7 *vs.* 4.7 ± 1.6 days, p = 0.1)	LAC 35 ± 159 total OME postop CA 633 ± 293 total OME postop p < 0.0001
Gatherwright et al., 2018 (PRS)	Clinical Trial	Unilateral delayed deep inferior epigastric perforator flap reconstruction	Bupivacaine or On-Q pump or historical control anesthetic (CA)	n_{total} = 27 n_{LB} = 8 (30) n_B = 8 (30)	LB 266 mg B 2 mg/kg QP 0.01 g/hour of 0.25%	Decrease in total narcotic use for LB group (Mean 0.08 *vs.* 0.18 *vs.* 0.10 *vs.* 0.31 mg/kg/day, p = 0.002)	**LB:** 40.9 OME total postop **Control:** Bupivacaine 79.9 OME total postop

				n_{QP} = 5 (18) n_{CA} = 6 (22)	bupivacaine	No difference in pain scores between LB group and B group (3 *vs.* 3 VAS score) Decrease in LOS in LB group (Mean 3.38 *vs.* 3.63 *vs.* 3.8 *vs.* 3.83 days, p = 0.08)	Q Pump 53.2 OME total postop CA 97.6 OME total postop *p > 0.05*
Breast Cancer Procedures with Breast Reconstruction							
Abdelsattar et al., 2016 (Ann Surg Oncol)	Retrospective review	Bilateral mastectomy with immediate TE reconstruction	PVB of non-liposomal bupivacaine + epinephrine	n_{total} = 97 n_{LB} = 53 (55) n_{CA} = 44 (45)	LB 20 mL (266 mg) PVB 6–10 mL bupivacaine + E (1:400,000)	Decreased opioid consumption in LB group (mean ± SD 9.4 ± 16.4 vs. 24.8 ± 23.9 OME, p < 0.001) No difference in LOS (83.0 vs. 77.3 %, p = 0.5 for d/c within 36h)	**LB:** 9.4 OME total postop **Control:** 24.8 OME total postop p = 0.03

						Decreased pain scores in LB group (mean ± SD 3.2 ± 1.8 *vs.* 4.2 ± 1.5, p = 0.008) Decreased postop time to first opioid dose in LB (210 ± 212 *vs.* 125 ± 171 min, p = 0.04)	
Butz et al., 2015 (PRS GO)	Retrospective review	Mastectomy with immediate implant-based breast reconstruction, with or without lymph node dissection	Nondepot bupivacaine pain pumps or patient-controlled intravenous/oral narcotics	n_{total} = 90 n_{LB} = 30 (33) n_{NDB} = 30 (33) n_{CA} = 30 (33)	LB 20 mL (266 mg) NDB NR IV Narcotics NR	No difference in LOS (mean ± SD 34.2 ± 16.2 *vs.* 41.5 ± 21.4 *vs.* 45.2 ± 18.4 hours, p = 0.074) Increased 1-day discharge in LB group (20 *vs.* 13 *vs.* 9, p = 0.016) No difference in analgesic consumption	**LB:** 1137 MME total postop **Control:** 1275 MME total postop with nondepot bupivacaine 1205 MME total

						(mean ± SD 1137 ± 508 *vs*. 1275 ± 580 *vs.* 1205 ± 500 ME, p = 0.605) Decrease in pain scores at 24 hours in LB group (p < 0.01)	postop with oral narcotics p = 0.605 (ns)
Jabloka et al., 2017 (Plast Reconstr Surg)	Retrospecti ve review	Mastectomy with immediate microsurgical breast reconstructio n (majority immediate)	Standard narcotic-based pain control regimen without locoregional anesthesia or TAP with local anesthetic	n_{total} = 128 n_{LB} = 40 (31) n_{TAP} = 48 (38) n_{CA} = 40 (31)	LB 20 cc of 1.3% LB TAP 2 cc/hour of 0.25% B CA NR	Decrease in mean LOS in LB group (mean ± SD 2.65 ± 0.66 *vs.* 3.52 ± 0.92 *vs.* 4.05 ± 1.26 days, p < 0.0001) Decrease in opioid consumption postop day 3 in LB group (mean ± SD 2.23 ± 4.12 *vs.* 3.60 ± 4.35 *vs.* 16.0 ± 26.83 IV-ME, p = 0.0181)	**LB:** 17.73 IV-ME total postop **Control:** 38.02 IV-ME total postop TAP 194.4 IV-ME total postop standard p = 0.0181

Nelson et al., 2021 (Ann Surg Onc)	Retrospective review	Abdominally based autologous free-flap breast reconstruction (majority immediate)	Intraoperative ketorolac	n_{total} = 601 n_{LB} = 274 (46) n_{K} = 109 (18)	NR	Increased patients with low postop opioid consumption compared to high in LB group	**LB:** 60.1% of patients were in low postop opioid consumption group (32.0 ± 15.5 OME total postop) **Control:** 31.4% of patients were in the low postoperative opioid consumption group 41.1 ± 19.5 OME total postop

							p = 0.003
Rendon et al., 2022 (PRS GO)	Retrospective review	Autologous breast reconstruction (majority immediate)	Historical control anesthetic (CA) or TAP with continuous local anesthetic (LA) catheter	n_{total} = 145 n_{LB} = 39 (27) n_{LA} = 60 (41) n_{CA} = 46 (32)	LB 266mg LA NR CA NR	No difference in pain scores between LB and CA groups Decrease in total OME between LB and CA groups (211.0 CI 154.8 to 267.2 *vs.* 518.4 CI 454.2 to 582.7, p < 0.001) Decrease in LOS for LB and LA groups (median 3.0 *vs.* 3.0 *vs.* 4.0 days, p < 0.001)	**LB:** 211.0 OME total postop **Control:** LA 215.9 CI 165.4 to 266.3 CA 518.4 CI 454.2 to 582.7 p < 0.001
Salibian et al., 2018	Retrospective review	Microsurgical Breast Reconstruction (majority immediate)	Bupivacaine injection with epinephrine	n_{total} = 114 n_{LB} = 50	LB 40 cc of diluted (20 cc of 1.3% LB with 80 cc of injectable	Decreased pain scores in LB group (mean ± SD 3.3 ± 0.2 *vs.* 4.3 ± 0.2, p < 0.0001)	**LB:** 25.9 ± 2.3 **Control:** 44.4 ±

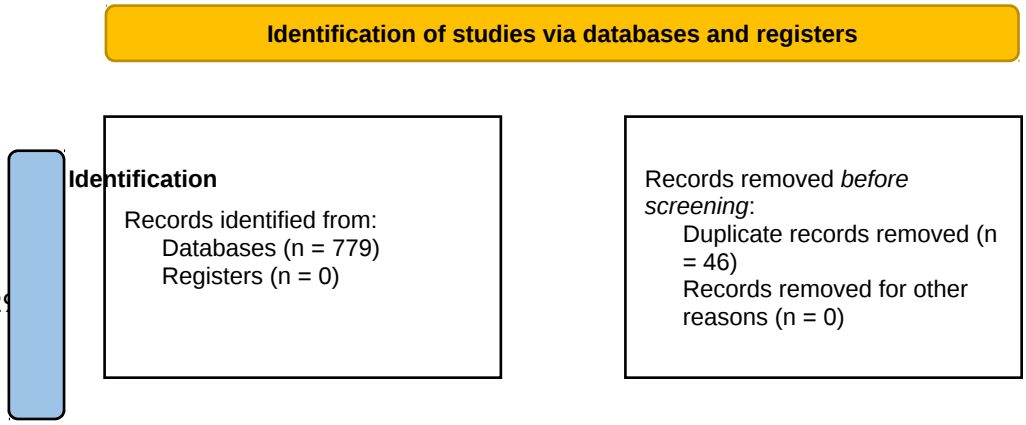
				(44) n_B = 64 (56)	saline) B Epi 0.25% bupivacaine with 1:100,000 epinephrine	Decreased overall opioid consumption in LB group (mean ± SD 25.9 ± 2.3 *vs.* 44.4 ± 4.0 IV-ME, p < 0.0001) No difference in LOS (mean ± SD 3.9 ± 0.1 *vs.* 4.2 ± 0.1 days, p = 0.1608)	4.0 p < 0.0001
Oncologic Mastectomy Only without Reconstruction							
Sarcon et al., 2022 (The American Surgeon)	Retrospective study	Total mastectomy (uni and bilateral) without lumpectomy	Intercostal nerve or soft tissue infiltration of non-liposomal bupivacaine	n_{total} = 712 n_{LB} = 512 (72) n_{CA} = 63 (9) n_{none} =	NR	B compared to LB showed no difference in hospital opioid consumption (OR of 1.16, 95% CI .62 to 2.19, p = 0.64) Patients had 2.1 hr shorter	**LB:** 1.4 OME/hr 37.4 OME total postop **Control:** 1.8 OME/hr 31.3 OME total postop

				137 (19)		LOS with B when compared LB, p = 0.0259	p = ns
Downes et al.	Retrospective review	Total mastectomy (uni and bilateral), lumpectomy	Ropivacaine, Non-liposomal bupivacaine	n_{total} = 417 n_{LB} = 148 (36) n_B = 69 (17) n_R = 200 (48)	NR	R was associated with a significantly reduced LOS ($p < 0.005$) and total OMME ($p < 0.005$) compared to bupivacaine. Patients given R had significantly lower pain scores than those given LB ($p < 0.005$)	**LB:** 18.75 OME/hr 60 OME total postop **Control:** 13.6 OME/hr with (bupivacaine) 45 OME total postop with (bupivacaine) 17.3 OME/hr with (ropivacaine) 45 OME total postop (ropivac

							aine) p = 0.0104

Reference	Selection	Detection	Reporting	Risk of bias
Smoot 2011	+	+	+	Low
Minkowitz 2012	+	+	+	Low
Haddock 2021	+	?	+	Some concerns
Kalaria 2018	+	+	+	Low
Ha 2019	+	+	+	Low
Lombana 2022	-	+	+	Some concerns
Gatherwright 2018	+	+	+	Low
Abdelsattar 2016	+	+	+	Low
Butz 2015	-	+	+	Some concerns
Jabloka 2017	+	+	?	Some concerns
Nelson 2021	+	+	-	Some concerns
Rendon 2022	+	+	+	Low
Salibian 2018	+	+	+	Low
Sacron 2022	+	+	+	Low
Downes 2021	+	?	+	Some concerns

Supplementary File



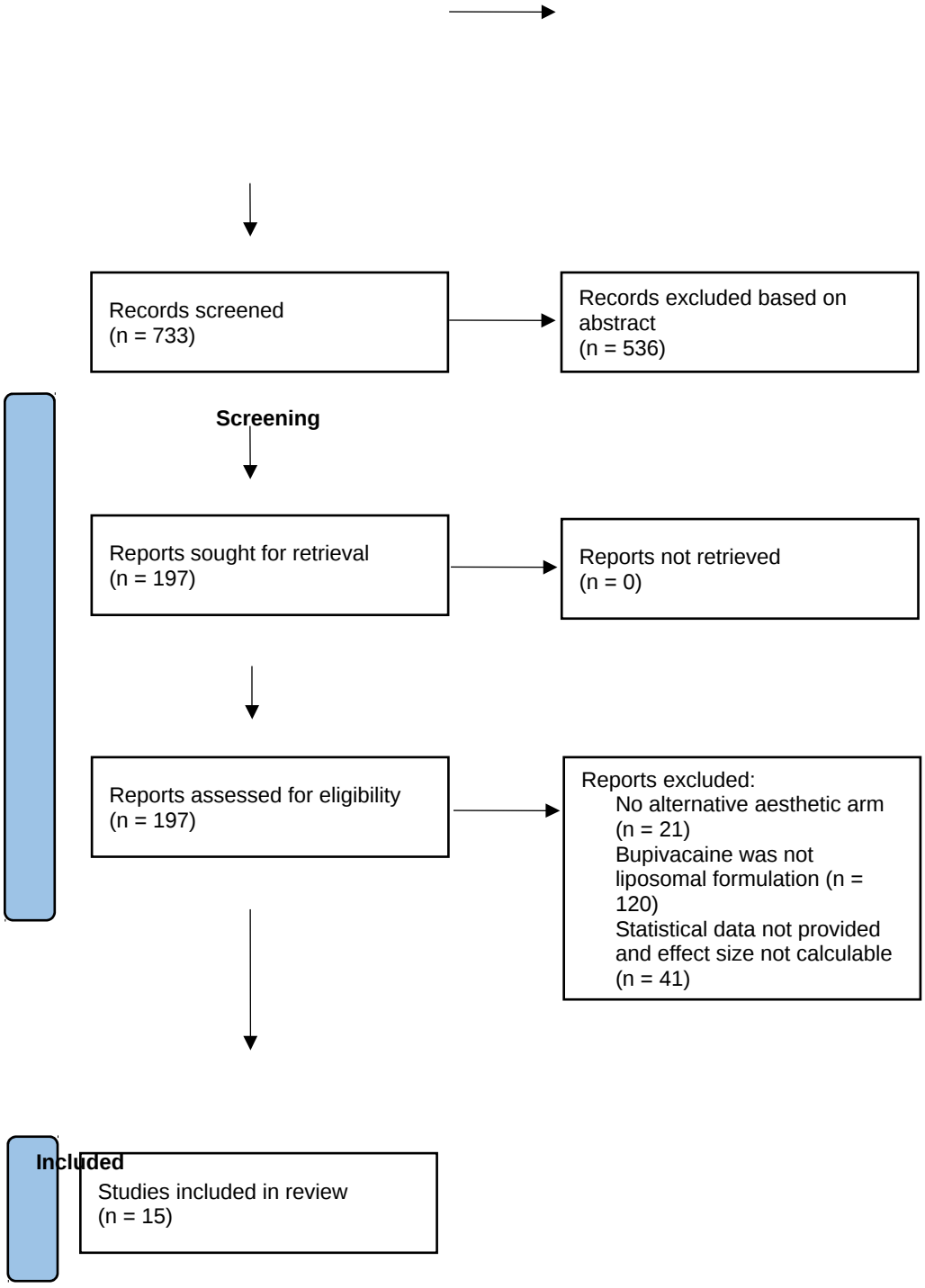

Records screened
(n = 733)
Records excluded based on abstract
(n = 536)
Screening
Reports sought for retrieval
(n = 197)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 197)
Reports excluded:
No alternative aesthetic arm (n = 21)
Bupivacaine was not liposomal formulation (n = 120)
Statistical data not provided and effect size not calculable (n = 41)
Included
Studies included in review
(n = 15)

Figure S1. PRISMA 2020 flowchart of selected studies. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/