Emerging Longer-Acting Local Anesthetic Formulations for Plastic Surgeons

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With the backdrop of a deteriorating opioid epidemic, multimodal intraoperative and postoperative analgesia represent an imperative practice for plastic surgeons to adopt.[1,2] Nerve blocks have come to represent an essential component in a plastic surgeon's armamentarium for reducing postoperative pain through direct and predictable inhibition of peripheral nociceptive signaling.[1] Indeed, our group has previously reported on significant reductions in postoperative opioid consumption, postoperative pain, PACU stay, nausea and vomiting, and duration of hospitalization associated with nerve block use in breast plastic surgery.[2]

Specific choice of local anesthetic agents within nerve blocks also carries great significance, and although there exists ample evidence and research on traditional local anesthetic agents, research into novel longer-acting formulations, such as liposomal bupivacaine and dexamethasone-bupivacaine mixtures, remains a relatively nascent practice.

Liposomal bupivacaine, an anesthetic formulation in which bupivacaine is encapsulated by multivesicular liposomes, has been reported to promise 96 hours of sustained anesthetic release.[2] Motakef et al have demonstrated superior efficacy of liposomal bupivacaine relative to bupivacaine alone in blocks targeting supraclavicular and intercostal nerves in breast surgery, whereas a randomized control trial by Gatherwright et al demonstrated superior efficacy of liposomal bupivacaine relative to bupivacaine when used in transversus abdominis plane (TAP) blocks.[3,4] Despite being associated with a significantly greater cost ($315 USD per 366 mg per 20-mL vial, vs $5.24 USD per 75-mL vial of bupivacaine), cost minimalization analyses have demonstrated that reductions in length of stay, hospital costs, and 30-day admission rates may contribute to more favorable economic profiles associated with liposomal bupivacaine use.[5] In contrast, more recent studies have failed to identify definitive analgesic advantages of this formulation, and interstudy comparisons, by means of meta-analyses, remain limited by lack of standardization of postoperative pain management across studies, institutions, and anatomic regions examined.[6] Certainly, more modest cost profiles of longer-acting anesthetic formulations than that of liposomal bupivacaine would facilitate greater adoption, and by extension, further insight and definitive evidence regarding whether longer-acting anesthetic formulations should come to represent the new standard of care.

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Table 1. Available Studies Directly Evaluating and Comparing the Analgesic Efficacy of Nerve Blocks With Liposomal Bupivacaine vs Dexamethasone-Bupivacaine Formulations

Bibliometrics	Objective	Patients	Results
Orthopedic Surgery			
Kim et al (2022) *Anesthesiology* doi:10.1097/ALN.0000000000004111	RCT Determine the analgesic efficacy of liposomal bupivacaine with bupivacaine and dexamethasone for patients undergoing ambulatory arthroscopic shoulder surgery. Interscalene block.	*n* = 112 LB (*n* = 55) Bupivacaine + dexamethasone (*n* = 56)	The LB group was associated with lower pain scores than the bupivacaine + dexamethasone group. There was no significant difference in opioid consumption, block duration, sensory and motor block resolution, patient satisfaction, block success, readiness for PACU discharge, PACU length of stay, or adverse events between the two groups.
Baessler et al (2020) *J Bone Joint Surg Am* doi:10.2106/JBJS.20.00225	RCT Determine the analgesic efficacy of liposomal bupivacaine compared to bupivacaine and dexamethasone in patients undergoing arthroscopic rotator cuff repair. Interscalene block.	*n* = 76 Bupivacaine + dexamethasone (*n* = 26) LB + bupivacaine (*n* = 24) LB + bupivacaine + dexamethasone (*n* = 26)	LB had lower narcotic use compared to formulations without LB. No significant difference in narcotic use between LB + bupivacaine with or without the addition of dexamethasone. There was no significant difference in VAS across formulations after controlling for covariates.
Colorectal Surgery			
Truong et al (2021) *Dis Colon Rectum* doi:10.1097/DCR.0000000000002008	RCT Determine the analgesic efficacy of liposomal bupivacaine compared to bupivacaine, epinephrine, and dexamethasone in patients undergoing minimally invasive colorectal surgery. TAP block	*n* = 102 LB (*n* = 51) Bupivacaine + dexamethasone + epinephrine (*n* = 50)	There was no significant difference in postoperative narcotic use, VAS, time to ambulation, length of hospitalization, complications, or readmissions between groups.

LB, liposomal bupivacaine; PACU, postanesthesia care unit; RCT, randomized controlled trial; TAP, transversus abdominis plane; VAS, visual analogue scale.

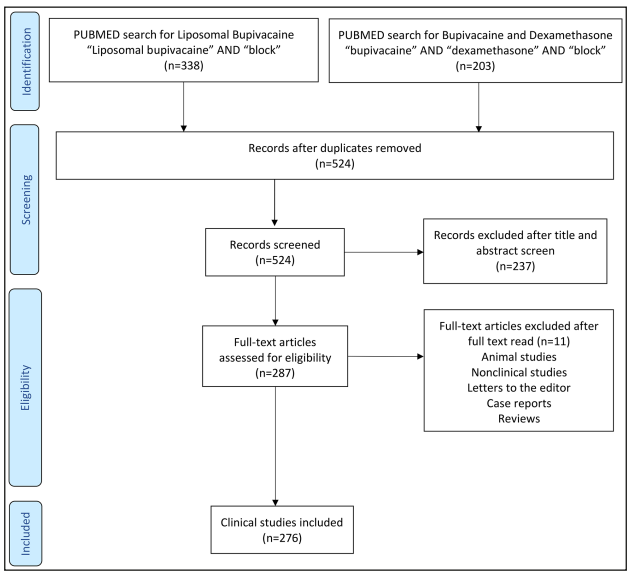

Figure 1. Systematic review flow chart in accordance with the preferred reporting items for systematic reviews and meta-analyses.

An alternative yet significantly cheaper longer-acting formulation is bupivacaine-dexamethasone mixtures, which comes at only a fraction of the cost of liposomal bupivacaine ($5.24 USD per 75 mL of bupivacaine vial and $0.44 USD per 1 mL of dexamethasone). This formulation has been increasingly studied in the surgical literature, albeit not within plastic surgery. Through a hypothesized inhibitory effect of dexamethasone on nociceptive pain fibers, upregulation of inhibitory potassium channels, and a regional decrease in blood flow to slow the dissipation of an infiltrated anesthetic, the majority of published randomized control trials in the orthopedic, gynecologic, and general surgery literature have demonstrated promising outcomes associated with bupivacaine-dexamethasone mixtures relative to bupivacaine alone, through prolonged durations of analgesia and decreased opioid consumption.[7] A recent study by Taylor et al was the first in plastic surgery to report on use of bupivacaine-dexamethasone blocks, demonstrating significant reductions in postoperative pain in patients undergoing reduction mammaplasty receiving this formulation in pectoralis nerve blocks.[7]

The question remains whether dexamethasone-bupivacaine formulations can provide non-inferior clinical and/or analgesic

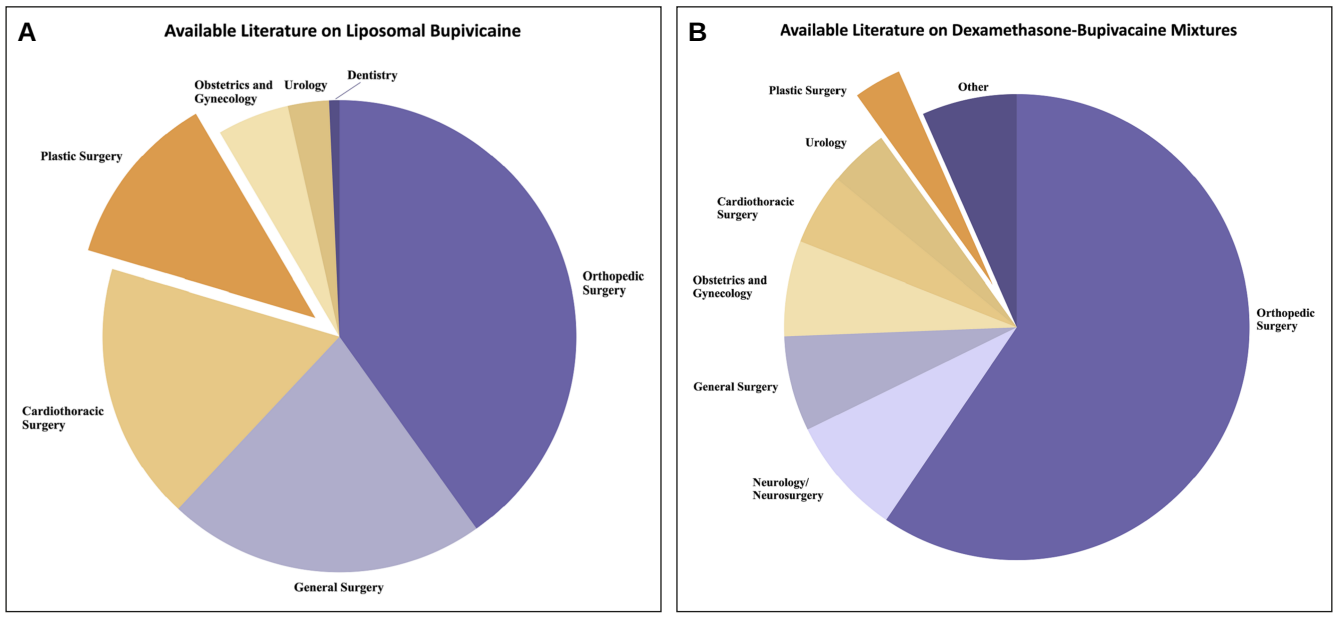

Figure 2. Proportions of available literature on (A) liposomal bupivacaine and (B) dexamethasone-bupivacaine mixtures when used within nerve blocks. Original articles investigating the clinical and analgesic efficacy of nerve blocks of the aforementioned formulations were included; reviews, case reports, and editorials were excluded.

benefits relative to liposomal bupivacaine, but at a fraction of the cost. If differences in efficacy and durations of action do exist, are they clinically significant, and more importantly, do they justify the significantly greater cost associated with liposomal bupivacaine?

Only 3 studies have ever directly compared outcomes from nerve blocks with bupivacaine-dexamethasone formulations vs liposomal bupivacaine, with contradictory findings (Table 1). Two studies from the orthopedic surgery literature yielded conflicting results with interscalene nerve blocks, whereas another study from the colorectal surgery literature concluded no significant differences between the two formulations in postoperative narcotic usage, pain, time to ambulation, length of hospitalization, complications, or readmission rates (Table 1).

We performed a systematic review of the literature to evaluate the evidence on novel long-acting local anesthetic formulations (Figure 1). To our surprise, we found that plastic surgeons lag far behind colleagues from other surgical specialties, with only 12% of the literature on nerve blocks with liposomal bupivacaine and 3% of literature on nerve blocks with dexamethasone-bupivacaine mixtures produced by plastic surgeons (Figure 2).

Plastic surgeons remain well-positioned to investigate and report on evolving practices in nerve blocks, given our specialty's deep understanding of surgical and neurovascular anatomy. Evaluating and establishing cost effective longer-acting local anesthetic formulations will not only promise improved outcomes and recovery for our patients but also may contribute to our societal responsibility as plastic surgeons to help combat the opioid crisis. Well-designed prospective trials directly comparing clinical outcomes and economic profiles associated with dexamethasone-bupivacaine formulations vs liposomal bupivacaine directly are indicated, especially within plastic surgery. It is the authors' wish that the present letter may thus serve as a catalyst on this front.

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