Original Article

Liposomal bupivacaine does not decrease postoperative opioid use or length of hospital stay in patients undergoing anterior cervical discectomy and fusion

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Background: Despite its widespread use, definitive data demonstrating the efficacy of liposomal bupivacaine (LB) is limited especially in patients undergoing anterior cervical discectomy and fusion (ACDF). Therefore, this investigation examined whether ACDF patients who received intra-operative LB (LB cohort) exhibited decreased post-operative opioid use and lengths of hospital stay (LOS) compared to ACDF patients who did not receive intra-operative LB (controls).

Methods: Eighty-two patients who underwent primary ACDF by a single surgeon from 2016 to 2019 were identified from an institutional database. Fifty-nine patients received intra-operative LB while twenty-three did not. Patient characteristics, medical comorbidities, complications, post-operative opioid consumption, and LOS data were collected.

Results: The LB cohort did not require fewer opioids on post-operative day (POD) 0, POD1, POD2, or throughout the hospital course after normalizing by LOS (total per LOS). The number of cervical vertebrae involved in surgery, but not LB use, predicted opioid consumption on POD0, POD1, and total per LOS. For every vertebral level involved, 242 additional morphine milligram equivalents (MME) were consumed on POD0, 266 additional MME were utilized on POD1, and 130 additional MME were consumed in total per LOS.

Conclusions: ACDF patients who received intra-operative LB did not require fewer post-operative opioids or exhibit a decreased LOS compared to controls. Patients whose procedures involved a greater number of cervical vertebrae were associated with greater opioid consumption on POD0, POD1, and total per LOS. ACDF patients, especially those who had a high number of vertebrae involved, may require alternative analgesia to LB.

Keywords: Analgesia; pain control; length of hospital stay (LOS); opioids; cervical spinal surgery

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Introduction

Despite widespread awareness regarding the opioid epidemic in the United States, related morbidity and mortality continue to pose an important public health burden (1). As the third highest prescribers of opioids, orthopaedic surgeons face increasing pressure to limit narcotic prescriptions and utilize alternative methods of pain control (2,3). This is especially true in spinal surgery, where up to 18.3% of opioid-naïve patients and 52.0% of patients who have pre-operative opioid use continued to use narcotics one year following their procedure (4). Furthermore, opioid use prior to cervical, thoracolumbar, and lumbar spinal surgery is associated with worse patient-reported outcomes at both three and twelve months post-operatively (5). Analgesic adjuncts, such as dexmedetomidine (6) and ketamine (7), have been shown to decrease acute post-operative opioid consumption although benefits may be limited in patients using opioids prior to surgery (8). Other therapies, including gabapentinoids (9), such as gabapentin and pregabalin, as well as erector spinae plane blocks (10), have yielded similar positive outcomes regarding post-operative pain following spinal surgery.

Another agent rapidly growing in popularity is liposomal bupivacaine (LB), a local anesthetic peri-operatively infiltrated into the surgical site to promote postoperative analgesia (11). Bupivacaine mitigates pain signaling acutely by blocking voltage-gated Na^+ channels, thereby inhibiting action potentials propagated by nociceptors. Evidence has also shown that bupivacaine reduces chronic pain via attenuation of central sensitization by inhibiting N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord (12). The liposomal formulation augments the duration of action by encapsulating bupivacaine in a collection of vesicles comprised of an aqueous core surrounded by a phospholipid bilayer that slowly release the drug as the lipids are metabolized (13). Although LB is relatively new, its incorporation into the post-operative analgesic armamentarium has been rapid for musculoskeletal surgery. Recent literature has shown LB to decrease opioid consumption in the acute post-operative period following many orthopaedic surgeries including total hip arthroplasties (THAs) (14), total knee arthroplasties (TKAs) (15), rotator cuff repairs (16), and open reduction internal fixation of distal radius fractures (17).

Despite its widespread attention, definitive data demonstrating the efficacy of LB is limited (18), especially in patients undergoing anterior cervical discectomy and fusion (ACDF). Therefore, this investigation examined whether ACDF patients who received pre-operative LB (LB cohort) exhibited differences in: (I) post-operative complications; (II) post-operative opioid consumption; and (III) length of hospital stay (LOS) compared to ACDF patients who did not receive intra-operative LB (controls). In addition, we explored the influence of several other variables, including age, body mass index (BMI), and number of vertebral levels involved in surgery, on the amount of post-operative opioid utilization. We hypothesized that the LB cohort would experience fewer post-operative complications, consume fewer opioids post-operatively, and demonstrate a shorter LOS relative to a matching cohort. We also hypothesized that older age, greater BMI, and more vertebral levels involved in surgery would predict greater post-operative opioid consumption. We present the following article in accordance with the STROBE reporting checklist (available at https://jss.amegroups.com/article/view/10.21037/jss-22-34/rc) (19).

Methods

Study population

Patients who underwent primary ACDF by a single surgeon were identified from the electronic medical record (EMR) of a large multi-hospital health system. All surgeries were performed at a single academic tertiary care center between October 1, 2016 and November 9, 2019. Exclusion criteria included patients who were undergoing ACDF for an acute or pathologic fracture, staged procedures, or revisions. A total of 577 spinal surgery patients were identified, 82 of which met the inclusion criteria: primary ACDF for spinal stenosis, disc herniation, spondylolisthesis or any combination of the three. Patient demographics, comorbidities/medical history, and complications were obtained from the EMR. Cardiovascular disease included hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, history of myocardial infarction, and a history of a cerebrovascular accident. Respiratory disease included asthma, obstructive sleep apnea, chronic obstructive pulmonary disease, bronchiectasis, and a history of lung cancer. Antibiotic use following discharge was defined as prescriptions from the surgeon for suspected wound infections within the first two routine outpatient post-operative follow-up visits. Approval from the Northwell Health institutional review board was obtained prior to this investigation.

Table 1 Patient characteristics

Characteristics	LB (N=59), mean ± SD	Controls (N=23), mean ± SD	95% CI	P value	Effect size (g)
Age (years)	54.5±19.5	52.1±12.7	(–6.4, 11.2)	0.369	0.134
BMI (kg/m^2)	30.4±7.5	28.2±4.8	(–1.2, 5.6)	0.185	0.321
# of levels (# of vertebrae)	1.9±0.8	2.1±0.8	(–0.2, 0.6)	0.435	0.250
LOS (days)	3.3±1.6	3.2±2.8	(–0.9, 1.1)	0.833	0.050

LB, liposomal bupivacaine group; SD, standard deviation; CI, confidence interval; BMI, body mass index; LOS, length of hospital stay.

Patient characteristics

Fifty-nine patients received intra-operative LB (LB cohort) while twenty-three patients did not (matching cohort). The decision to utilize LB in some patients versus others was purely temporal. Beginning in 2018, the surgeon decided to incorporate the use of LB into his clinical practice; therefore, all ACDF patients in 2018 and 2019 received LB while those in 2016 and 2017 did not. These patients' characteristics are displayed in *Table 1*. There were 22 men in the LB cohort (37.3%) and 10 men in the matching cohort (43.5%; P=0.606). The mean age of the LB cohort was 54.5 versus 52.1 years in the matching cohort. Based on the BMI of the LB cohort (30.4 kg/m^2) and the matching cohort (28.2 kg/m^2), patients in both conditions were classified on average as overweight; however, there was no significant difference between them. Similarly, neither the number of vertebral levels involved in surgery (1.9 versus 2.1), nor the LOS (3.3 versus 3.2 days) between the LB cohort and the matching cohort, respectively, demonstrated significant differences.

Patient comorbidities related to their indications for surgery and baseline medical history are displayed in *Table 2*. The frequency of radiculopathy, myelopathy, spinal stenosis, disc herniation, and spondylolisthesis did not significantly differ between the LB and the matching cohort. Likewise, the prevalence of cardiovascular disease, respiratory disease, type II diabetes mellitus, current tobacco smoking, and preoperative opioid usage, also did not significantly differ between cohorts.

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Northwell Heath (IRB# 19-0792) and individual consent for this retrospective analysis was waived. Patients were partitioned into two cohorts: one that received intra-operative LB (Exparel, Pacira Pharmaceuticals, Parsippany, NJ, USA) and one that did not. All patients in both cohorts received a subcutaneous injection of 0.25% bupivacaine hydrochloride into the surgical site prior to incision. Only patients in the LB cohort received an additional 10 milliliters of LB via injection into the subcutaneous tissues surrounding the incision prior to wound closure. Post-operative opioid consumption on post-operative day (POD) 0, POD1, and POD2 as well as LOS were obtained from the EMR. Total opioid usage throughout the entire LOS and the total opioid usage normalized by LOS (total per LOS) were calculated dosages of all opioid medications and were transformed into morphine milligram equivalents (MME) using the following conversions: morphine intravenous (IV) (1 mg =1 MME), morphine per os (PO) (3 mg =1 MME), tramadol PO (50 mg =1 MME), oxycodone PO (2 mg =1 MME), hydrocodone PO (3 mg =1 MME), hydromorphone PO (0.75 mg =1 MME), hydromorphone IV (0.15 mg =1 MME), subcutaneous fentanyl (0.04 mg =1 MME), and fentanyl IV (0.02 mg =1 MME) (20). For patients who received patient-controlled analgesia (PCA), IV hydromorphone was delivered at either a 0.5 mg bolus or run as an infusion of 1 mg/mL at a rate of 30 mL/h. PCA was discontinued when patients subjectively expressed adequate pain control.

Post-operative analgesia protocol

Beginning in the post-anesthesia care unit, the following pain medications were prescribed through the duration of the hospital stay: acetaminophen 975 mg PO every 8 hours, tramadol 50 mg PO every 8 hours, oxycodone 5 mg PO every four hours as needed for mild-to-moderate pain (1 to 6 on the visual analog scale), oxycodone 10 mg PO every four hours as needed for severe pain (7 to 10 on the visual analog scale), one-time hydromorphone 0.5 mg IV as needed for breakthrough pain, and cyclobenzaprine

Table 2 Patient comorbidities and complications

Variables	LB (N=59), n (%)	Controls (N=23), n (%)	RR	95% CI	P value
Comorbidities					
Radiculopathy	44 (74.6)	13 (56.5)	–	–	0.120
Myelopathy	18 (30.5)	10 (43.5)	–	–	0.306
Spinal stenosis	35 (59.3)	18 (78.3)	–	–	0.129
Disc herniation	46 (78.0)	19 (82.6)	–	–	0.768
Spondylolisthesis	2 (3.4)	1 (4.3)	–	–	1.000
Cardiovascular disease	33 (55.9)	16 (69.6)	–	–	0.321
Respiratory disease	15 (25.4)	5 (21.7)	–	–	1.000
Diabetes mellitus (Type II)	16 (27.1)	4 (17.4)	–	–	0.408
Current smoker	11 (18.6)	4 (17.4)	–	–	1.000
Preoperative opioid use	24 (40.7)	11 (47.8)	–	–	0.437
Complications					
Seroma	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
Dural tear	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
Wound dehiscence	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
DVT	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
PE	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
ICU transfer	2 (3.4)	0 (0)	2.00	(0.10, 40.14)	0.651
UTI	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
SSI	0 (0)	0 (0)	0.40	(0.01, 19.59)	1.000
Antibiotic use after D/C	1 (1.7)	2 (8.7)	0.19	(0.02, 2.05)	0.189
Readmission within 30 days	1 (1.7)	0 (0)	1.20	(0.05, 28.44)	0.910

LB, liposomal bupivacaine group; RR, relative risk; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; UTI, urinary tract infection; SSI, surgical site infection; D/C, discharge.

5 mg PO three times a day as needed for muscle spasms. Gabapentin 100 mg PO three times a day was ordered beginning at 6 AM on POD1 and also continued throughout the hospital stay. If the patient's pain was deemed by the surgeon to be insufficiently controlled on this regimen, the acute pain management service was consulted, who then decided if PCA was clinically appropriate.

Statistical analyses

Descriptive statistics are presented as means [standard deviations (SDs)]. Statistical significance was determined based on α=0.05, and all tests were two-tailed. Comparisons between categorical data were conducted via Fisher's exact tests; accompanying relative risk was calculated for complications. Continuous variables were first assessed for normality via Shapiro-Wilk tests. Because none deviated significantly from normality, Welch's *t*-tests were then utilized to compare means. Effect sizes were measured by Hedges' g. Due to the lack of statistical significance, it was deemed unnecessary to strictly control the familywise error rate. Multiple linear regressions were also performed to explore potential predictors of post-operative opioid consumption. All analyses were conducted in Excel (Microsoft Corporation®, Redmond, Washington, USA) and SPSS (version 27.0; IBM, Armonk, New York, USA). Due to the lack of literature that both mimics the design of the present study and provides the data necessary for

Table 3 Postoperative opioid consumption

Opioid use (MME)	LB (N=59), mean ± SD	Controls (N=23), mean ± SD	95% CI	P value	Effect size (g)
POD0	374.9±578.2	477.0±561.6	(–178.5, 382.7)	0.471	0.178
POD1	454.1±783.2	461.7±677.7	(–362.1, 377.3)	0.970	0.010
POD2	121.9±205.5	128.8±189.2	(–91.5, 105.3)	0.914	0.034
Total	918.7±1,470.4	987.4±1,299.2	(–628.6, 766.0)	0.845	0.048
Total per LOS	269.9±458.8	343.8±552.2	(–164.0, 311.8)	0.538	0.152

MME, morphine milligram equivalents; LB, liposomal bupivacaine group; SD, standard deviation; CI, confidence interval; POD, postoperative day; total, total opioid consumption throughout the entire hospital course; total per LOS, total opioid consumption throughout the entire hospital course after normalizing by length of stay.

power analysis, sample size was estimated to be 68 patients per cohort (assuming α=0.05 and β=0.2) using the post-operative opioid consumption and lengths of stays reported in a previous retrospective cohort study (21).

Results

Post-operative complications

Complications following surgery were rare (*Table 2*). There were no reported cases of seroma, dural tear, wound dehiscence, deep vein thrombosis (DVT), pulmonary embolism (PE), urinary tract infection (UTI), or surgical site infection (SSI). Two patients in the LB cohort were post-operatively transferred to the surgical intensive care unit (SICU), one for weakness and one for hypotension requiring vasopressors; both fully recovered without deficits or further complications. One patient in the LB cohort and two in the matching cohort were prescribed antibiotics (cephalexin) at their first post-operative visit for surgical site erythema and serous discharge. These patients did not meet Centers for Disease Control and Prevention (CDC) criteria for an SSI (22), and their signs resolved over the next several days. One patient in the LB cohort was readmitted within 30 days for persistent vomiting and diarrhea secondary to viral colitis who fully recovered following an uncomplicated hospital course. There were no significant differences in risk of any complications between cohorts.

Post-operative opioid consumption

Post-operative opioid usage is displayed in *Table 3*. The LB and matching cohorts and controls consumed 374.9 versus 477.0 MME on POD0, 454.1 versus 461.7 MME on POD1, and 121.9 versus 128.8 MME on POD2. There were no significant differences in opioid usage between cohorts on any POD. Similar results were obtained regarding the total opioid consumption throughout the entire hospital course and the total per LOS. The LB cohort used a total of 918.7 MME while the matching cohort required 987.4 MME. When normalized per LOS, the LB cohort consumed a total of 269.9 MME while the controls utilized 343.8 MME. These data further suggest that no significant differences in inpatient post-operative opioid consumption existed between cohorts.

LOS

LOS is shown in *Table 1*. In the LB cohort, LOS was 3.3 versus 3.2 days in the matching cohort. This data suggests that there was no significant difference in LOS between cohorts.

Predictors of post-operative opioid consumption

Multiple linear regression involving sex, age, BMI, number of vertebral levels, and LB use was employed to predict pos-operative opioid consumption. The number of cervical vertebrae involved in the procedure significantly predicted opioid use on POD0 (β=241.7; 95% CI: 87.8, 395.6; P=0.002), POD1 (β=265.5; 95% CI: 58.0, 473.0; P=0.013), and total per LOS (β=130.3; 95% CI: 37.3, 223.3; P=0.007), but sex, age, BMI, and LB use did not. For every vertebral level involved, approximately 242 additional MME were consumed on POD0, roughly 266 additional MME were utilized on POD1, and approximately 130 additional MME were consumed throughout the hospital course after normalizing by LOS. None of the aforementioned independent variables significantly predicted opioid consumption on POD2.

Discussion

This study sought to evaluate whether LB was an effective analgesic adjunct, that is, to reduce the amount of acute post-operative opioid consumption, for patients undergoing primary ACDF. In this analysis, patients who were treated with intra-operative LB failed to demonstrate decreased post-operative narcotic use on POD0, POD1, and POD2 compared to patients who did not receive LB. Additionally, the use of LB was not associated with a decrease in LOS. The results did show that the number of vertebral levels involved in surgery predicted the total postoperative opioid consumption normalized per LOS. This might make intuitive sense, as more extensive surgeries require more surgical instrumentation, a larger surgical field, and longer operative times, which are all likely to increase post-operative pain and the need for immediate analgesia.

Clinically, the utility of LB is appealing due to its safety as well as socio-economic implications. Considering the persistent high incidence of opioid overdose-related deaths (23), alternative methods of pain control including local anesthetics have become particularly attractive in part due to their longer duration (half-life of LB =24 to 34 hours) (24), which may ameliorate the post-operative opioid burden. Maintaining adequate analgesia while concurrently limiting opioid consumption remains a high priority in spinal surgery, for these medications heighten the risk of respiratory depression, delirium, as well as the potential for long-term misuse. While the individual risk of prescription opioid misuse following spinal surgery is relatively low, it continues to be a concern for certain patients (25). Alternative analgesics (e.g., LB) have been used as a method to decrease the amount of narcotics needed in the immediate post-operative period, thereby decreasing patient opioid exposure and potentially lessening the downstream contribution of spinal surgery-related narcotics to the opioid epidemic. However, those desired acute effects were not achieved in our study population. Another factor to consider when assessing the use of LB is the financial burden. With a manufacturer price of $136.00 for 10 milliliters, there is a relatively high cost associated with the use of LB compared to other agents (26). Considering that the results of this study demonstrated that LB did not decrease acute post-operative opioid consumption or LOS, the use of this agent may not be cost-effective in patients undergoing primary ACDF.

This investigation is the first to examine the effects of LB on post-operative opioid consumption in patients undergoing primary ACDF, although there have been similar studies addressing LB in other types of spinal surgery (21,27-31). For example, LB has been included as a component of enhanced recovery after surgery (ERAS) protocols in posterior cervical surgery (27). A retrospective case series of 99 patients who underwent posterior cervical decompression and fusion showed that an ERAS protocol including intraoperative intramuscular LB did not shorten LOS or improve discharge disposition compared to a non-ERAS protocol without LB (27). Results comparable to those in the present study regarding the effectiveness of LB can also be found elsewhere in spine literature. For example, in a randomized control pilot trial of 50 patients undergoing primary posterior lumbar decompression and fusion, Brown *et al.* demonstrated that the use of LB was not effective in decreasing opioid consumption in the first three PODs or overall LOS (28). While this investigation looked at posterior lumbar surgery and not cervical, their conclusions mirrored those in the present study. Similarly, in a retrospective cohort study of 52 posterior cervical decompression and fusion patients and 64 posterior lumbar decompression and fusion patients, Grieff *et al.* reported that LB did not decrease peri-operative narcotic use or LOS compared to bupivacaine HCl alone in either the cervical or lumbar cohort (20). In a mixed prospective and retrospective cohort study of 80 patients undergoing single-level lumbar microdiscectomy, Puffer *et al.* noted that LB infiltration allowed earlier weaning of intravenous narcotics; however, there was no difference in total MME consumed or visual analog scale (VAS) scores (29). Furthermore, Cloyd *et al.* examined the effects of LB on perioperative opioid use in 141 pediatric patients undergoing spinal deformity surgery, and concluded that LB was not associated with reductions in postoperative opioid use (30). While the pediatric population is notably different from adults, similar findings raise additional concern regarding the efficacy of LB.

While the spinal surgery literature supports the conclusions of the present study, in other orthopaedic subspecialties, the evidence is mixed. In a multicenter randomized controlled trial of 139 patients undergoing TKA, Dysart *et al.* found that local infiltrations of LB with bupivacaine HCl demonstrated a 91% reduction in opioid consumption and 19% decrease in pain intensity compared to bupivacaine HCl alone during the first 24 hours following surgery (31). In contrast, a similar investigation by Schroer *et al.* of 111 TKA patients concluded that

periarticular injection with LB was not superior to plain bupivacaine injection in improving pain scores or decreasing narcotic use during hospitalization (32). Further, a 2021 meta-analysis performed by Ji *et al.*, in a systematic review of randomized control trials did not necessarily demonstrate superior postoperative pain as compared to other analgesic agents (33). Beachler *et al.* reported a mild decrease in opioid consumption in THA patients injected with LB compared to controls; however, there was no difference in LOS, and given that the narcotic reduction amounted to less than 1 pill, the cost of LB injections may not be justified (34). In contrast, Yu *et al.* concluded that as part of a multimodal pain control protocol involving LB, THA patients demonstrated decreased postoperative opioid requirements and earlier time to beginning physical therapy. As a result, they argue for its widespread use (35). These divergent findings suggest a strong need for additional research especially randomized controlled trials.

The present investigation possesses several limitations. Notably, this was a retrospective analysis focused on examining the body of work of a single surgeon. While this allows for the surgeries to be relatively standardized, it does require caution in generalizing the results to all ACDF patients as there is surgeon procedural variability. Another limitation from the involves the lack of post-operative pain scores, e.g., VAS, due to their absence in the EMR. Future studies should include VAS scores which would further elucidate the possible role of LB during ACDF. Additionally, we were not able to stratify patients quantitatively (only qualitatively) based on pre-operative opioid use. That is, we procured documentation of whether study participants used opioids prior to surgery or not (i.e., opioid naïve) but not the amount of MME consumed. This factor deserves consideration as prior opioid sensitivity or misuse can affect the quantities of narcotic medications required for effective analgesia. Pre-operative opioid consumption is associated with not only greater opioid requirements during hospitalization but also inferior patient outcomes overall (5). Future investigations should consider surveying patients for prior opioid use and exploring the potential effects of LB in this population.

Conclusions

We have shown that intra-operative use of LB did not lead to a decrease in post-operative opioid use on POD0, POD1, or POD2 in patients undergoing primary ACDF. There was no difference in LOS in patients treated with LB compared to those who were not. Furthermore, this study demonstrates that opioid consumption increased as the number of operative vertebral levels increased. Surgeons performing primary ACDF should carefully consider the cost-benefit analysis of LB as its efficacy in reducing the acute opioid burden appears limited.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jss.amegroups.com/article/view/10.21037/jss-22-34/rc

Data Sharing Statement: Available at https://jss.amegroups.com/article/view/10.21037/jss-22-34/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jss.amegroups.com/article/view/10.21037/jss-22-34/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Northwell Heath (IRB# 19-0792) and individual consent for this retrospective analysis was waived.

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