

Pain Management Efficacy Study Between Continuous and Single-Administration Bupivacaine Following Lumbar Spinal Fusion

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Poorly managed postoperative pain decreases patient satisfaction, impedes early patient mobilization, lengthens inpatient hospital stay, and increases healthcare costs. Multimodal analgesia with local anesthetics is considered most effective for postoperative pain management. This study compared patients undergoing lumbar fusion who received plain bupivacaine from May 2011 until August 2012 with those who received liposomal bupivacaine from September 2012 until May 2013. The aim was to determine which preparation reduced postoperative opioid use the most. All lumbar spinal fusion surgeries in the periods indicated were included in the study. Ninety-three patient charts were reviewed: 47 for the plain bupivacaine group and 46 for the liposomal bupivacaine group.

The study found no statistical difference between liposomal and plain bupivacaine in providing postoperative pain control from lumbar fusion surgery. Liposomal bupivacaine is as effective as plain bupivacaine for postoperative pain control after lumbar fusion. However, a continuous infusion system carries substantial inherent drawbacks: need for training and setup, pump cost, risk of infection at the insertion site, or catheter migration. Therefore, liposomal bupivacaine becomes the logical and attractive choice to manage postoperative pain following lumbar fusion.

Keywords: Bupivacaine, liposomal bupivacaine, pain management, postoperative pain, single-administration bupivacaine.

Opioids remain the gold standard in postoperative pain management. However, multimodal analgesia, with the use of local anesthetics, is considered the most effective method for postoperative pain management with the goals of maximizing pain relief and decreasing unwanted side effects due to opioid use.¹⁻⁵ Although the administration of bupivacaine, an amide local anesthetic, is part of multimodal analgesia in the management of postoperative pain following lumbar spinal fusion, liposomal bupivacaine (LB) preparation has not been investigated in neurosurgery, specifically in spinal fusion. This study hopes to fill the gap and provide scientific evidence in the utility of liposomal bupivacaine in the management of pain following lumbar spinal fusion.

Patients undergoing surgical procedures may suffer substantial persistent postoperative pain.^{1,6} The degree of postoperative discomfort due to lumbar spinal fusion, with pain scores ranging from 6 to 10 on a 10-point scale, varies with the technique and approach used.^{7,8} Minimally invasive procedures, because of substantially less manipulation of underlying structures, result in less postoperative back pain.³ In contrast, the longer incision and increased complexity of a multilevel lumbar spinal fusion may predispose the patient to relatively high pain levels in the postoperative period.⁷

Pain is a normal protective physiologic response to an adverse chemical, thermal, or mechanical stimulus.^{4,9} Poorly managed postoperative pain can contribute to substantial morbidity and mortality.¹⁰ In addition, it decreases patient satisfaction, impedes early patient mobilization, lengthens inpatient hospital stay, and increases healthcare costs.^{3,6,11-13} Furthermore, adverse physiologic effects from poorly managed postoperative pain may affect every organ system in the human body. These physiologic effects include hypertension, tachycardia, increased systemic vascular resistance, enhanced myocardial irritability, increased myocardial oxygen demand, and possibly myocardial ischemia.¹⁴ Respiratory consequences of undermanaged postoperative pain can be equally devastating for the patient. Shallow breathing associated with pain can cause atelectasis and contribute to the development of pneumonia postoperatively.¹⁴ These physiologic effects can result in a delay in the patient's ability to resume activities of daily living or an overall delay in the patient's recovery as well as in substantial postoperative morbidity and mortality.⁹

Although clinical evidence suggests that besides the well-recognized analgesic activity of opioids, unwanted and potentially major adverse side effects from opioid use may limit their utility. Such unwanted side effects include nausea, vomiting, somnolence, constipation,

postoperative ileus, respiratory depression, hypoxia, and oversedation.^{3,4,10,11,14-16} Furthermore, opioids may cause confusion, hypoventilation, dry mouth, itching, urinary retention, opioid tolerance, and opiate-induced hyperalgesia among other detrimental effects.¹⁰

Use of local anesthetics as part of a multimodal approach to pain management has become increasingly popular and is proven efficacious. When local anesthetic is injected in sufficient concentration and close to the nerve, local anesthetic molecules travel across neuronal cell membrane to block pain conduction, preventing pain transmission. The dose of local anesthetic administered and its systemic absorption, tissue distribution, and drug elimination profoundly affect its plasma concentration. Although systemic absorption and the peak plasma level are directly proportional to the amount of local anesthetic deposited, the rate of absorption, and thus the degree of blockade, differs with each local anesthetic.⁹ Bupivacaine, with its high lipid solubility and protein binding, produces a much longer duration of action and is ideal for surgical wound infiltration as part of multimodal analgesia.¹⁰

The purpose of this study was to compare efficacy of pain management in patients undergoing lumbar spinal fusion receiving either plain bupivacaine (PB) delivered through continuous infusion via an indwelling delivery system or those receiving bupivacaine administered through a single dose of liposomal preparation, at the end of surgery as measured by total postoperative opioid use. In addition, the investigators aimed to determine whether this study would demonstrate a reduction in any of the following: the time for rescue analgesia, the incidence of opioid adverse events such as nausea and vomiting, pain intensity scores, total length of hospital stay, and total cost for pain management between the 2 groups.

Methods

This case-control, retrospective study consisted of convenience surgical patients who underwent lumbar spinal fusion from May 2011 until May 2013. The patient population consisted of those who received PB through a continuous delivery system (ON-Q Pain Relief System, Halyard Health Inc) from May 2011 until August 2012, and those who from September 2012 until May 2013 received single-dose LB infiltration. The continuous delivery system delivered 0.5% PB continuously, whereas up to 266 mg of diluted LB was infiltrated subcutaneously into the incision sites.

All lumbar spinal fusion surgeries within the period indicated were included in the study. Further patient disposition is displayed in Figure 1. The investigators arbitrarily agreed on randomization in the PB group. Every 5 charts were chosen for inclusion in the study for the PB group, while every 2 charts in-between were taken out of consideration from the study. No randomization was employed to the LB group because of its limited n. Because

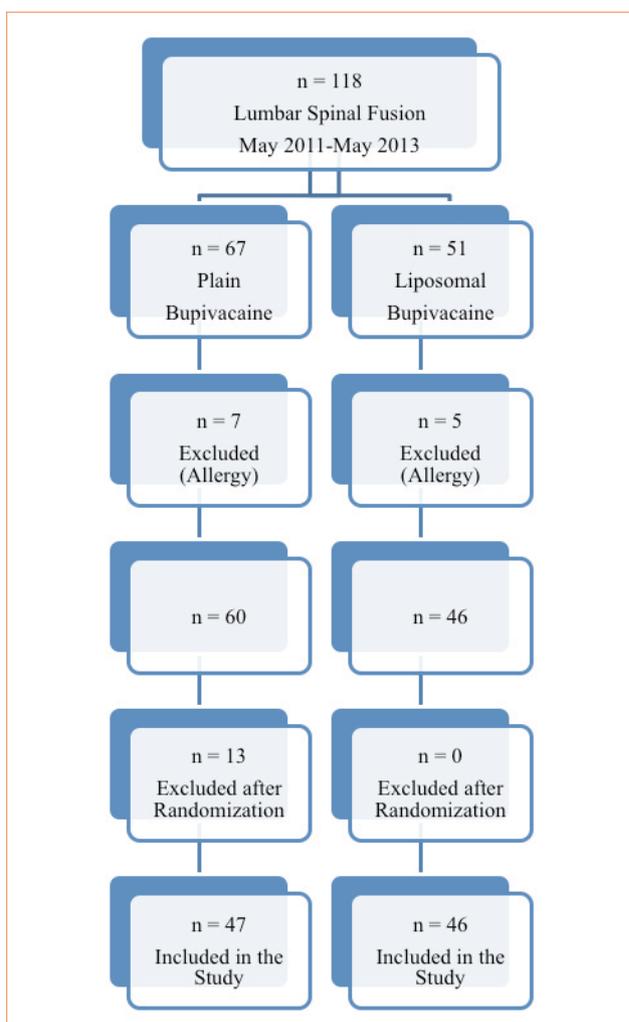


Figure 1. Patient Disposition

of the retrospective design of the study, informed consent was not applicable. Before data collection, a Health Insurance Portability and Accountability Act (HIPAA) waiver was submitted and approved by the institutional review board (IRB). In addition, the data collection tool was submitted and subsequently approved by the IRB. The investigation was initiated following IRB approval.

Patient charts were reviewed for demographic information (age, sex, diagnosis, comorbidities, medication profile) and intended variables. The primary outcome measure investigated was the difference in total opioid consumption within 72 hours following lumbar spinal fusion. Total opioid consumption is based on patient-controlled analgesia data and medication record (0-72 hours), converted to intravenous morphine equivalents using the Opioid (Opiate) Equianalgesic Conversion Calculator (<http://clinicalcalc.com/opioids/>). Data collection was timed from entry into the postanesthesia care unit (PACU) through 72 hours in the hospital.

Secondary outcome measures investigated were time to first rescue analgesia, incidence of postoperative

Dosing	Plain bupivacaine, mg	Liposomal bupivacaine, mg	P value ^a
Total 24 h	65.36 (47.13)	66.71 (52.29)	.895
Total 48 h	108.14 (79.46)	112.63 (103.25)	.814
Total 72 h	138.17 (135.38)	118.68 (76.11)	.456
Total opioid	283.63 (244.38)	269.14 (195.16)	.754

Table 1. Opioid Consumption

^aP value of $\leq .05$ considered statistically significant.

nausea and vomiting, average pain scores, and total length of hospital stay. Time to first rescue analgesia was recorded when the first opioid medication was administered, either while in the PACU or in the nursing unit. The incidence of postoperative nausea and vomiting was recorded per patient report. Numeric pain scores, recorded using the Numeric Pain Scale, were averaged through 72 hours; total length of hospital stay, in hours, was summed from time of admission to time of discharge. The total cost of postoperative pain management was based on pharmacy equivalency on the acquisition cost of PB, LB, and morphine at the time of study.

The research design had sufficient statistical power based on the α set at .05 and power of 0.80. The study is composed of independent cases and controls with 1 control per case. Prior data indicate that the probability of exposure among controls is 0.5 based on a 35% reduction in opioid consumption 72 hours following lumbar spinal fusion. If the true probability of exposure among cases is 0.3, we will need to study 47 case patients and 47 control patients to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.8. The Type I error probability associated with this test for this null hypothesis is .05. We used an uncorrected χ^2 statistic to evaluate this null hypothesis.

Descriptive statistics for all continuous (mean \pm SD) and categorical [N (%)] data were calculated. To compare the differences between the 2 study groups regarding opioid side effects, an uncorrected χ^2 was performed to evaluate the H_0 : There is no significant difference in the opioid consumption following lumbar spinal fusion between groups. Student *t* test was used to compare total opioid consumption, hospital length of stay, and time for rescue analgesic. All analyses were performed using SPSS for Windows version 19.0 (IBM Corp). A 2-tailed *P* level of .05 was considered statistically significant in all analyses.

The simple imputation method was employed by carrying forward the last available objective data. Eight pain scores (1.89% of the total number of pain scores) were imputed for the PB group, while 6 pain scores (1.45%) were imputed for the LB group.

Results

A total of 93 patient charts were reviewed: 47 for the

PB group and 46 for the LB group. The primary efficacy outcome, total opioid consumption through 72 hours, showed no statistically significant difference between groups ($P = .754$; Table 1). This supports the null hypothesis put forth by the study that there is no difference in the total opioid consumption between groups. This finding is corroborated by the results of Hollander et al,¹⁷ who compared LB with subfascial continuous local anesthesia after laparoendoscopic single-site donor nephrectomy. When we compared groups for age and gender, we found no significant differences either (Table 2). Although both groups have a relatively higher proportion of males, but not significantly different, no previous studies suggest gender-related pharmacodynamic or pharmacokinetic differences in efficacy following administration of either bupivacaine preparations.

The impact of rescue medication to manage postoperative pain on treatment effect is critical. In addition, the time for when rescue medication is used accounts for a meaningful comparison between groups. The median time for first administration of a rescue opioid on arrival to the PACU was not statistically significant when PB was compared with LB ($P = .325$). Furthermore, time for subsequent rescue opioid was not statistically significant ($P = .636$). Conversely, other studies demonstrated significant differences in the median time to first opioid use were the proportion of patients who received opioid rescue medication much later was significantly greater in the LB group: 14.3 hours vs 1.2 hours, $P < .0001$ (Gorfine et al¹⁸); 19 hours vs 8 hours, $P = .005$ (Haas et al¹⁹); 7.2 hours vs 4.3 hours, $P < .0001$ (Golf et al²⁰); and 9.9 hours vs 2.7 hours, $P < .0001$ (Dasta et al²¹).

Adverse events were defined as incidents of nausea and vomiting occurring after administration of opioid medication on entry in the PACU through 72 hours. Although incidents of nausea and vomiting were noted in both groups, no significant difference was found ($P = .510$). However, Haas et al¹⁹ reported an incidence of adverse events of 4% for LB compared with 35% with PB ($P = .007$), and Dasta et al²¹ reported 20% incidence of adverse events in the LB group compared with 36% in the PB group ($P < .0001$). Gorfine et al¹⁸ reported an incidence of 16.8% adverse events after administration of LB vs 18.1% for the placebo group, while Golf et al²⁰ reported 59.8% in the LB group vs 67.7% for placebo.

Opioid consumption	Plain bupivacaine, mg		Liposomal bupivacaine, mg		P value ^a
	Mean (SD)	P value ^a	Mean (SD)	P value ^a	
Age, y	50.3 (12.6)	—	54.8 (12.4)	—	.096
Total 24 h	n = 27 M, 20 F		n = 25 M, 21 F		.895
Male	66.90 (38.56)	.794	69.55 (62.76)	.689	.852
Female	63.29 (57.59)		63.16 (36.53)		.993
Total 48 h	n = 27 M, 20 F		n = 25 M, 21 F		.814
Male	113.96 (68.11)	.560	118.00 (126.31)	.697	.884
Female	100.39 (93.71)		105.55 (64.05)		.841
Total 72 h	n = 27 M, 20 F		n = 25 M, 21 F		.456
Male	137.52 (89.56)	.974	124.41 (69.10)	.689	.631
Female	138.98 (179.88)		113.85 (83.13)		.587
Total opioid	n = 27 M, 20 F		n = 25 M, 21 F		.754
Male	284.00 (184.05)	.990	267.17 (216.50)	.941	.761
Female	283.10 (315.58)		271.59 (170.25)		.887

Table 2. Opioid Consumption per Age and Gender

^aP value of $\leq .05$ considered statistically significant.

Postoperative time, h	Plain bupivacaine		Liposomal bupivacaine		P value ^a
	Mean	SD	Mean	SD	
0	2.021	0.887	2.370	1.040	.083
2	2.776	0.848	2.978	0.802	.235
4	2.939	0.944	3.130	0.748	.278
6	2.959	0.978	3.087	1.007	.532
12	3.163	0.897	3.239	1.036	.703
24	2.958	0.898	3.023	0.952	.739
36	3.106	0.698	2.977	1.067	.494
48	3.095	0.905	3.000	0.771	.616
72	3.185	0.681	3.419	0.564	.158
Overall	2.895	0.931	3.011	0.962	.090

Table 3. Pain Scores

^aP value of $\leq .05$ considered statistically significant.

Individual patient rating of pain was assessed using the Numeric Pain Scale. The scores, ranging from 0 to 10, were averaged for 72 hours postoperatively. When overall pain scores were compared between the PB and LB groups, this study observed no statistically significant difference ($P = .090$; Table 3). Both Haas et al¹⁹ and Dasta et al²¹ reported significantly lower cumulative pain scores 72 hours after surgery ($P < .05$ and $P = .039$, respectively). Similarly, when LB was compared with placebo, studies by Gorfine et al¹⁸ and Golf et al²⁰ demonstrated significantly lower pain scores ($P < .0001$ through 72 hours and $P = .0005$ through 24 hours, respectively).

Although this efficacy study measured the outcome variables through 72 hours, hospital length of stay, in hours, was measured through the day of discharge.

No significant difference was observed between the 2 groups: 83.63 hours in the PB group vs 88.53 hours in the LB group ($P = .456$). In addition, given this observation, it can be deduced that although pharmacy acquisition cost varies by more than 50%, with LB being more expensive than PB, total cost for pain management within 72 hours after a lumbar spinal fusion was not statistically significant.

Because of the lack of statistical significance found during univariate analyses, the investigators deemed that no multivariate regression analysis was necessary.

Discussion

The goal of multimodal therapy for postoperative pain management is to maximize the efficacy and duration of the analgesic effect, while at the same time minimiz-

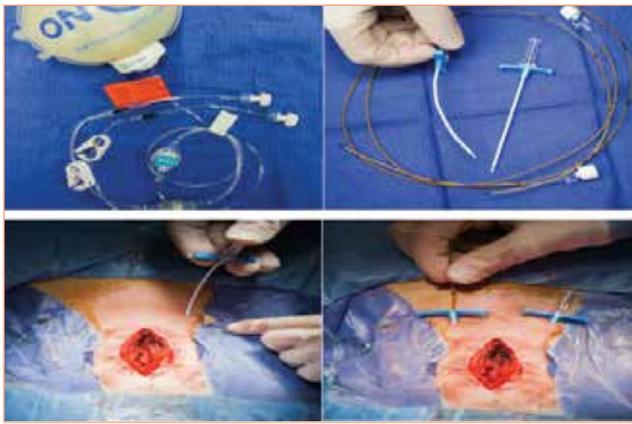


Figure 2. Continuous Delivery System for Local Anesthetic (ON-Q Pain Relief System)^a

^aUsed by permission of Halyard Health Inc.

ing opioid use and its unwanted adverse side effects. However, the relatively short duration of action of local anesthetics used for multimodal analgesia makes them less than ideal for long-term analgesia.²² Duration of analgesia may be brief, and single injections may not provide long-term benefits in terms of pain relief.³ The use of local anesthetic via an elastomeric pump delivery system (eg, On-Q) into the subfascial aspects of the surgical wound allows for continuous infusion. This results in lower postoperative pain scores and reduced narcotic use.³ Various surgical procedures such as inguinal hernia repair, spine surgery, cardiothoracic surgery, plastic surgery, iliac crest bone harvest, cesarean delivery, laparotomy, laparoscopy, and orthopedic procedures have resulted in statistically significant reduction in pain scores and opioid use in the postoperative period with the continuous delivery system.^{3,5}

The ON-Q Pain Relief System (Figure 2) is composed of a catheter and an elastomeric pump that automatically and continuously delivers a regulated flow of medication, such as PB, to and around surgical wound sites at a pressure of 10 psi. The catheter contains multiple holes along the infusion segment distributed in a spiral pattern to provide 360° drug infusion, which occurs between the black tip and the first marking above the tip.²³ The pump is filled with 400 mL of PB; the dosage is 5 mL/h and can be increased up to 6 mL/h depending on the patient's individual pain relief requirements. The catheter is removed once the infusion is complete.

However, major drawbacks exist with such a continuous infusion delivery system. The use of indwelling catheters requires setup and comes with a need for increased training and added cost of the pumps.⁴ Additionally, the use of catheters introduces the risk of infection, septicemia, intravascular placement, or intravascular catheter migration.^{4,22,24} Therefore, to avoid these risks, interest has focused on liposomal technology in delivering local anesthetics.



Figure 3. Administration of Liposomal Bupivacaine

The advent of LB in an injectable suspension provides an extended pain relief in a single administration while decreasing the need for supplemental opioids in the postoperative period. Liposomal bupivacaine is intended for single-dose administration with a recommended dose, either concentrated or diluted up to 1:14, based on the size of the surgical site, volume required to cover the area, and individual patient factors that may influence the safety of an amide local anesthetic. Liposomal bupivacaine is a sterile, nonpyrogenic, white to off-white, preservative-free aqueous suspension of multivesicular liposomes containing bupivacaine at a concentration of 13.3 mg/mL. Liposome bupivacaine contains approximately 3% extraliposomal bupivacaine, allowing for fast onset of analgesia.²⁵ The maximum dose is 266 mg (20 mL) and should be injected slowly with a 25-gauge or larger-bore needle into the soft tissues (Figure 3) of the surgical site, with frequent aspiration to check for blood and minimize the risk of intravascular injection.²⁵

Liposomal technology has been used effectively to slowly control the release of drugs such as antifungals, antineoplastic agents, antibiotics, morphine sulfate, and cytarabine.^{4,24,26,27} Liposomes are microscopic capsules consisting of a phospholipid outer bilayer encasing an aqueous core,^{4,24} which encapsulates water-soluble drug in a honeycomb-like structure. The outer lipid layer releases the drug contained in the inner core over a desired period, up to 72 hours.⁴

Studies have demonstrated that single-dose administration of LB reduced pain score intensity. Haas et al¹⁹ demonstrated a significantly lower mean total postoperative opioid consumption ($P = .019$) in a posthemorrhoidectomy pain study using LB compared with PB, both as local infiltration. In a pooled analysis from 9 studies representing 5 different surgical procedures, Dasta et al²¹ reported a 35% decrease in the average amount of opioid consumed when LB was used compared with PB (12.2 mg vs 19.0 mg, $P < .0001$).

Gorfine et al¹⁸ compared bupivacaine extended-release liposomal injection in a placebo-controlled trial

of patients undergoing hemorrhoidectomy and reported a statistically significant difference in the mean total amount of opioid rescue medication (morphine equivalents) consumed through 72 hours, 22.3 mg vs 29.1 mg ($P \leq .0006$). Similarly, when 120 mg of LB was compared with placebo in patients who underwent bunionectomy, Golf et al²⁰ reported a statistically significant difference in the number of patients who avoided use of opioid rescue medication through 24 hours, 7.2% vs 1.0% ($P = .0404$).

Conclusion

Substantial postoperative pain is commonly associated with lumbar spinal fusions and is most often treated with opioids and various adjuncts that have a multitude of adverse side effects. These side effects can complicate a patient's hospital stay. Poorly managed postoperative pain decreases patient satisfaction and results in increased healthcare costs. Appropriate postoperative pain management is crucial in promoting earlier patient mobilization, shortening the inpatient length of stay, and reducing healthcare costs. The use of local anesthetics as part of multimodal analgesia is considered the most effective method for postoperative pain management, maximizing the duration and efficacy of analgesia while simultaneously minimizing opioid use and its myriad adverse side effects.^{16,21,28}

The efficacy results observed in this study found that LB is as effective as PB in providing postoperative pain management from lumbar fusion surgery. However, the use of continuous infusion anesthetic via a delivery system carries inherent major drawbacks. Single-administration LB, with its minimal side effect profile and proven efficacy in the realm of postoperative pain management, makes it a logical and attractive choice for use in lumbar spinal fusion surgeries. Moreover, while this study investigated patients undergoing lumbar spinal fusion, the results may be extrapolated to other surgical patient populations, especially those with multiple comorbidities and those who may not tolerate opioid use for acute postoperative pain.

The study investigators identified few limitations, including the study's retrospective nature and the lack of true control for patient selection and binding as seen in a prospective study. Although both treatments were well tolerated, patient satisfaction may be one variable interesting to validate if this were a prospective study. Additionally, the consistency among different caregivers for which the pain scores were observed and recorded cannot be validated. Finally, as with all pain efficacy studies, the subjective nature of pain perception may limit accurate interpretation of individual assessments regarding the efficacy of LB and PB.

This study provides a framework for future studies and offers an opportunity for a prospective, larger, randomized study either in neurosurgery or general surgery

where the use of LB may be warranted. Moreover, when proved efficacious compared with conventional postoperative pain management, LB may become a mainstay in the arsenal of postoperative analgesia with the potential to reduce opioid burden during early recovery.

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DISCLOSURES

The authors have declared no financial relationships with any commercial interest related to the content of this activity. The authors did not discuss off-label use within the article.