texas orthopaedic journal®

ORIGINAL RESEARCH

Efficacy of Liposomal Bupivacaine for Postoperative Pain after Spine Surgery

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ABSTRACT

Introduction: Pain control following spine surgery can be challenging. Recently, there has been increasing interest in the use of multimodal pain regimens, including local perioperative analgesia, over postoperative narcotic use.
Methods: Twenty-four patients undergoing spine surgery from August 2013 to September 2014 received liposomal bupivacaine (LB) intraoperatively. The type of surgery, age, and BMI were used to match the experimental group with twenty-four control patients between July 2012 and August 2013. The length of hospital stay, postoperative pain scores and postoperative opioid requirements were compared between the two groups.
Results: The median length of hospital stay was 1 day in the LB group and 2 days in the control group. The VAS score was 3.3 and 5.7 at 0-6 hours, 3.3 and 6.2 at 6-24 hours, and 3.4 and 6.0 at 24-48 hours, for the LB and control group, respectively. The distributions of the mean VAS scores were significantly different at 0-6 hrs, 6-24 hours, and 24-48 hours, with smaller average VAS scores in the LB group. Median morphine equivalent use was 10.0 mg and 22.3 mg at 0-6 hours, 6.7 mg and 14.0 mg at 6-12 hours, 15.0 mg and 27.0 mg at 12-24 hours, and 31.3 mg and 30.0 mg at 24-48 hours, for the LB and control group, respectively
Discussion: We found a decrease in LOS, total narcotic usage, and patient-reported pain scores up to 48 hours postoperatively with the use of LB. These results suggest that LB can play a valuable role in decreasing LOS while improving pain control after routine spine surgery.
Level of Evidence: III; Case-control study.
Keywords: Liposomal bupivacaine; Spine surgery; Postoperative pain; Outcomes; Opioids.

INTRODUCTION

Pain control following spine surgery can be challenging. Uncontrolled pain postoperatively can influence a patient's recovery, outcome, and return to normal activity. In contrary, ineffective pain management can lead to longer hospital stay and even increase morbidity and mortality [1]. Addressing these pain management issues effectively can improve quality of life and higher patient satisfaction [2]. Recent approaches have favored multimodal pain regimens, including local perioperative analgesia,

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over postoperative narcotic and opioid use.

Opioids, although an effective postoperative pain management modality, are known to cause adverse side effects including nausea, dizziness, vomiting, urinary retention, constipation, ileus, pruritus, dyspnea, and sedation [3]. Local anesthetics have been utilized to help avoid these side effects, but the duration of pain control from a single dose can be limited. Recently, single-dose long acting local anesthetic injected around the wound perioperatively has been shown to be an effective method of postoperative analgesia [1]. Liposomal bupivacaine (LB) injectable suspension has gained popularity over the past few years for the treatment of pain and analgesia postoperatively. This new formulary releases LB using multi-vesicular liposomes as a delivery platform, which allows a delayed release of bupivacaine; this helps prevent accumulation of unexpectedly high blood and tissue concentrations of bupivacaine [4]. Perioperative use of LB can help decrease pain and opioid consumption postoperatively, allowing patients to mobilize sooner and decrease their length of stay [3,5-7]. Although the use of LB in general surgery and total joint arthroplasty has been extensively studied, a literature search revealed no prior clinical data in the setting of spine surgery.

With the rising costs of healthcare and subsequent decrease in reimbursement, hospitals have become more stringent approving relatively expensive drugs that do not have a generic version available. For this reason, our local pharmacy committee asked us to assess the pain control achieved with a trial of LB in spine patients prior to the possible approval of this formulation's use in our hospital. This study investigates the clinical results seen in patients given LB after spine surgery compared with a retrospective matched-control group where no local was used. The primary objective of this study was to estimate the length of hospital stay of patients who received LB perioperatively during spine surgery and compare this to patients who did not receive perioperative local anesthesia. Secondarily, we assessed postoperative pain scores and postoperative narcotic/opioid requirements.

MATERIALS & METHODS

Study Design

This is a retrospective matched case-control study. Patients receiving LB were matched to the controls using age, type of injury, surgery, and body-mass index (BMI).

Patients

This study was reviewed and approved by our hospital's institutional review board prior to initiation. Starting in August 2013, a consecutive series of patients undergoing spine procedures with incisions less than 8 cm were chosen to receive LB intraoperatively. A total of 24 patients received LB between August 2013 and September 2014. All patients undergoing spine surgery utilizing an incision less than 8 cm between January 2012 and August 2013 within this single level-1 trauma healthcare system who did not receive LB were then identified as a possible control group. Patients who had chronic regional pain syndrome, BMI more than 40, bleeding disorders, neuromuscular deficits, were chronic smokers, or were nonambulatory were excluded from this study. The LB patients were matched using age, type of surgery, and BMI classification. We matched one control per case for a total of

48 patients, 24 in the case group (LB) and 24 in the control group. Ages were matched to within 5 years in 19 patients. In 6 patients, no match was found within those parameters; hence, patients were matched as closely as possible. Type of surgery was matched utilizing ICD-9 codes. Levels were matched based on anatomic location. For fusions, number of levels and approach were matched appropriately, with the exact level within an anatomic location being the only variable (ie, lumbar and cervical fusions were matched accordingly). BMI was matched to within a value of 5 in 22 patients. In 2 patients, no match was found within those parameters, so patients were matched as closely as possible.

Interventions

Eight different spine surgeries were utilized. The breakdown was as follows: 5 patients underwent cervical instrumentation removal (22852), 1 underwent removal of lumbar instrumentation (22852), 9 had cervical laminoplasties with reconstruction of the posterior elements (63051), one C7-T1 transpedicular decompression with partial discectomy (63056), 16 had lumbar interbody fusions with nonsegmental instrumentation (22840), 5 had lumbar decompression with foraminotomy (63047), 4 had lumbar hemilaminectomy with laminotomy and/or discectomy (63030), 6 had laminectomies with exploration and/or decompressions (63047), and 1 had a partial resection of C7 and T1 spinous processes (22100).

The LB was mixed precisely for each patient in the following manner: 25 ml of 0.5% Marcaine with epinephrine was mixed with 20 ml of LB (266 mg) diluted with 55 ml saline, creating a total solution volume of 100 ml. Five 20cc syringes were then drawn up. Each patient in the LB group was injected with the five syringes of LB intraoperatively with a 20 gauge needle. Injections were administered in a meticulous manner as follows: 1 syringe injected in a fan-like manner into the left and right side of the wound subcutaneously (2 syringes total), 1 syringe in the paraspinal musculature with emphasis on blocking the medial nerve branch 1 level above and 1 level below on each side (2 syringes total), and ½ syringe evenly injected below the fascial level on each side (1 syringe total). The wound was then closed in the usual fashion and patients were taken to the post-anesthesia care unit (PACU) for postoperative care. All patients received as needed (pro re nata; PRN) opioids and narcotics. Patients not being admitted to the hospital were discharged home once the PACU discharge guidelines had been met.

The patients who had fusions or laminectomies were hospitalized for an average of 2 days. Initially, they were given either a morphine or hydromorphone patient-controlled analgesia (PCA) that was discontinued on postoperative day 1. Patients were then started on Norco, Tramadol, or Tylenol #3 tablets for the reminder of their stay, depending on patient preference and tolerability.

Outcome Measures

The medical records were reviewed and data collected including medical record number, date of birth, gender, surgery type, surgery date, surgeon involved, BMI, length of hospital stay, postoperative morphine equivalent use, visual analog scale (VAS) pain scores pre- and postoperatively, opioid side effects, wound complications, and mobility status postoperatively.

To convert opioids/narcotics into morphine equivalents, we utilized an opioid conversion chart commonly cited in

literature to convert all measurements into milligrams of morphine [8]. The morphine equivalent usage for each patient was then divided into the following time increments: 0-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, and 48 or more hours. VAS scores at each time point throughout the hospital stay were recorded. The median and maximum pain scores where then computed for each patient.

When collecting secondary variables from the chart, age, BMI, and sex were recorded directly from the chart.

Statistical Methods

Reporting of categorical variables was done with counts (percentages). Continuous variables were described with mean (standard deviation) (if approximately normal) or median (min-max) (if not normal). Paired t-tests were used for comparison of continuous variables by analgesic group, if the variables were approximately normal. If the variables were not normal, a Wilcoxon-Sign-Rank test was used. McNemar's tests were used for comparison of categorical variables. Tests were performed on the matching variables to confirm that the groups were similar for the matching variables. To account for the dependency of the repeated VAS scores the average VAS score was calculated per patient for each time period. These resulted on 24 independent observations per group for each time period. Wilcoxon-Sign-Rank test was used to compare the difference in distribution between cases and controls for these averages. A mixed effects model using the matches as clusters and all the times per individual was fitted to the model. Residuals were checked to assess the fit of the model and model assumptions. Software use for the analysis was SAS version 9.4 and StatXact v. 10.1.

RESULTS

Following review of all medical records and radiographs, 48 total patients met inclusion criteria within the spine group. Of these, there were 24 patients who received LB and 24 control patients who received no local analgesia.

The median length of stay was 1 day in the LB group and 2 days in the control group (p=0.0013). No differences in medication-related or surgical site complications were noted, and no readmissions occurred in the early postop period.

The median of the average VAS score was 3.3 (0.0-7.4) and 5.7 (3.0-8.5) at 0-6 hours; 3.3 (1.0-5.3) and 6.2 (2.4-9.0) at 6-24 hours; and 3.4 (1.3-6.9) and 6.0 (3.7-9.0) at 24-48 hours, for the LB and control group, respectively (only 2 patients stayed more than 48 hours so no comparison could be done for that time period). The distributions of the mean VAS scores were significantly different at 0-6 hours (p<0.0001), 6-24 hours (p=0.00624), and 24-48 hours (p=0.0059), with smaller average VAS scores in the LB group.

Median morphine equivalent use was 10.0 mg and 22.3 mg at 0-6 hours (p=0.0003), 6.7 mg and 14.0 mg at 6-12 hours (p=0.0352), 15.0 mg and 27.0 mg at 12-24 hours (p=0.0129), and 31.3mg and 30.0mg at 24-48 hours (p=0.7539), for the LB and control group, respectively. The median total medication usage was 25.9 mg in the LB group and 83.7mg in the control group (p=0.0015) (Table 1). One patient in the LB group and 2 patients in the control group developed wound infections 2.5-4 weeks after surgery, requiring an incision and drainage and a course of intravenous and oral antibiotics. One patient in the control group developed a draining sinus tract requiring removal of

hardware. One LB patient had increased pain and a recurrence of her radicular symptoms at her 6-week follow-up visit, but symptoms subsequently improved. Another patient in the LB group, and 1 patient in the control group experienced urinary retention while in the hospital, which resolved spontaneously.

Table 1. Baseline Characteristics of the Study Patients.

Parameter	LB (n=24)	SOC (n=24)	P Value
Matching Criteria			
Age	59 (18–72)	58.5 (20–69)	0.9099[€]
BMI	29.4 (3.8)	29.2 (4.0)	0.8359
Gender			
Male	9 (37.5%)	9 (37.5%)	1.0[#]
Female	15 (62.5%)	15 (62.5%)	
Outcomes			
Side Effects	3 (30.0%)	7 (70.0%)	0.3438[†]
Length of Stay	1 (0–4)	2 (0–5)	0.0013[†]
Preop VAS	7 (0–10)	5.5 (0–10)	0.3593[†]
Medication usage			
<6 hours	10.0 (0.0–40.7)	22.3 (6.7–73.3)	0.0003[†]
6-12 hours	6.7 (0.0–30.7)	14.0 (3.3–49.3)	0.0352[†]
12-24 hours	115.0 (0.0–33.3)	27.0 (2.0–117.3)	0.0129[†]
24-48 hours	31.3 (21.7–44.7)	30.0 (5.0–133.3)	0.7539[†]
>48 hours	56.7	20.0 (3.3–362.7)	*
Total	6.7 (0.0–30.7)	14.0 (3.3–49.3)	0.0352[†]
Average Pain Scores			
<6 hours	3.3 (0.0–7.4)	5.7 (3.0–8.5)	<0.0001
6-24 hours	3.3 (1.0–5.3)	6.2 (2.4–9.0)	0.0024
24-48 hours	3.4 (1.3–6.9)	6.0 (3.7–9.0)	0.0059
>48 hours	4.3 (3.0–5.5)	5.9 (3.0–9.0)	*

[€]Paired t-test; [#]McNemar's test; [†]Wilcoxon-sign-Rank test; *The LB group had only 1 observation for medication and only 2 for pain scores so no testing was possible.

DISCUSSION

Optimizing pain modalities after spine surgery can decrease a patient's postoperative opioid requirement, time to mobilization, pain-related morbidity, and increase a patient's quality of life [2]. Local anesthetic injected at the wound site perioperatively has gained popularity over the past 20 years for postoperative pain control in various surgeries. Multiple formulations have been studied, including ropivacaine, bupivacaine, and more recently LB. LB consists of bupivacaine encapsulated in aqueous chambers in the core of multivesicular liposomes.

This design allows the bupivacaine to be released over several days, thus allowing a controlled release of the drug [4]. To our knowledge, there are no published studies that specifically analyze LB in the setting of spine surgery. Our study specifically compared LB use intraoperatively to a control group where the standard of care for pain control was oral and intravenous narcotics. We found a statistically significant decrease in the length of stay, pain scores up to 48 hours, and morphine equivalent requirements within the first 24 hours for patients receiving perioperative LB compared to patients only receiving postoperative opioid/narcotic analgesics (Figure 1).

Recent literature has demonstrated mixed results regarding the efficacy and dosing of LB compared to multimodal drug regimens. One possible explanation for this

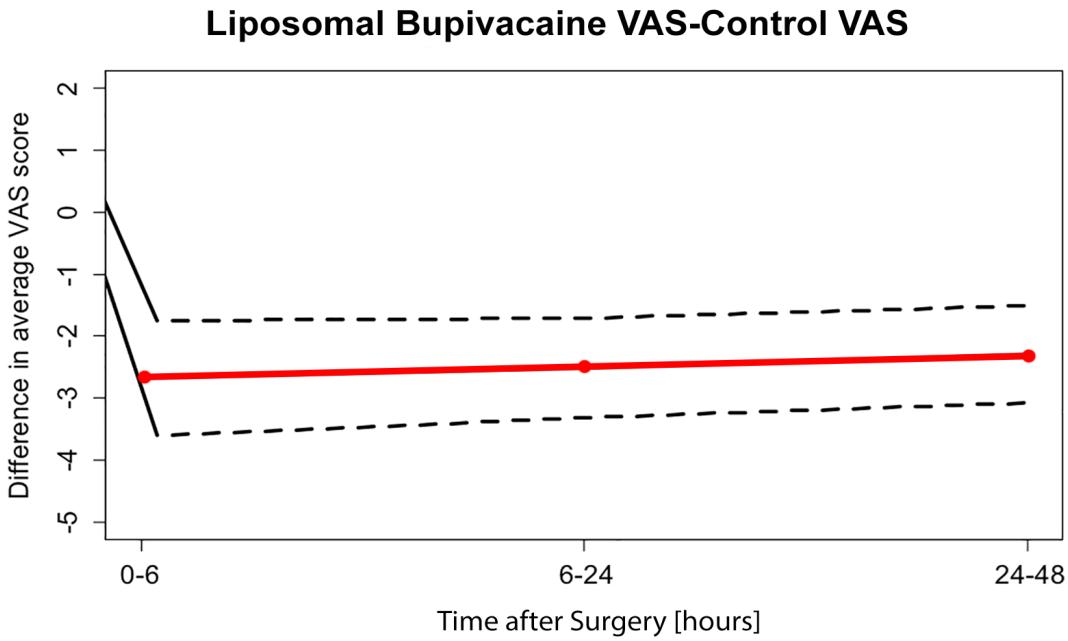

Figure 1. The red line represents the difference in average VAS scores over time period (LB-control). The dashed lines represent approximate 95% confidence bands. The figure shows that the average mean score for LB is constantly smaller than the control average VAS by about 2.4 points in the VAS scale.

may be the difficult method of injecting LB. LB is highly viscous and has little ability to diffuse through tissues. Careful administration with a small gauge needle to spread the preparation evenly in each tissue layer is mandatory to achieve consistent pain control. Several studies have indicated positive results with the use of LB. Golf et al [9] compared LB to a placebo injected after bunionectomy. They found significantly decreased pain scores at 24 hours ($p=0.0005$) and 36 hours ($p<0.0229$) postoperatively. Patients also avoided opioids at a greater rate in the LB group (7.2%) versus the placebo group (1%) postoperatively ($p<0.0404$). Gorfine et al [10] demonstrated DepoFoam bupivacaine significantly decreased the amount of opioid rescue drug used, time to initial use of a rescue drug, and the level of patient satisfaction at 72 hours postoperatively compared with a placebo.

Other studies have indicated mixed

or poor outcomes with LB compared with a control. Bramlett et al [11] compared multiple dose regimens of DepoFoam bupivacaine with bupivacaine HCl in patients undergoing total knee arthroplasty. They found statistically significant benefits with the DepoFoam bupivacaine 532 mg in cumulative pain scores at rest on Days 2, 3, 4, and 5, and on the assessment of a blinded-care provider's satisfaction with analgesia when compared with bupivacaine HCl. However, they found no significant differences in these outcomes for lower doses of DepoFoam bupivacaine. Bagsby et al [12] compared LB to a standard periarticular injection of ropivacaine, morphine, and epinephrine after total knee arthroplasty. Their results demonstrated a higher pain score after 24 hours in the LB group compared with the control group ($p=0.04$), while a lower percentage (16.9%) of patients in the LB group rated their pain as "mild" in comparison to the control group (47.6%).

Side effects of LB that have been reported in the literature include intervertebral disk cell cytotoxicity, myocyte toxicity, chondrotoxicity, and granulomatous inflammation [3,6]. We found minimal side effects in the patients who received LB. Several patients complained of postoperative nausea and vomiting requiring Zofran or Phenergan, which was not significantly different from the control group. Nausea and vomiting are known side effects of operative anesthetics and cannot necessarily be linked to LB use.

There are several limitations to our study. It is a retrospective study with a small sample size. All retrospective studies are limited by their ability to retrieve data, which is already stored in historical documentation. However, the electronic medical record at our institution captures scores at pain regular time points from the nursing staff, and all narcotic usage was similarly documented and easily searched. LB after spine surgery was only utilized with a small number of patients prior to evaluation by our pharmacy committee. It was not adequately powered to assess infrequent but potentially severe side effects of LB. For a more thorough understanding of LB's impact on a patient's length of stay and pain scores, a larger, prospective study is warranted. While great care was taken to match the LB patients to appropriate controls from the same surgeons, the surgeon's selection bias of determining when to use LB is possible.

CONCLUSIONS

We found a decrease in the length of stay, total narcotic usage, and patient-reported pain scores up to 48 hours postoperatively with the use of LB. These results suggest that when used for routine spine surgery, LB can play a valuable role in decreasing length of stay while at the same time improving pain control.

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