Liposomal versus plain bupivacaine for pain control following vaginal reconstruction

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Introduction: *Liposomal bupivacaine (LB) is a depot formulation of bupivacaine, which releases the drug over 72 hours to prolong local pain control. This retrospective study compares the effect of using LB versus plain bupivacaine on postoperative pain control, length of hospital stay and cost among patients undergoing vaginal reconstructive surgery.*

Materials and methods: *Patients who underwent vaginal reconstructive surgery with levatorplasty and received an injection of 20 cc of either plain bupivacaine or LB for pudendal nerve block were included. The primary outcomes included postoperative narcotic use and subjective pain score. The secondary outcome was postoperative length of stay. Comparisons between groups were performed using the T test, Mann Whitney U and Chi-square tests with $p < 0.05$ considered significant.*

Results: *Between June 2016 and December 2021, 25 patients had received LB as a pudendal nerve block and 25 had received plain bupivacaine. Demographics between groups were similar. There was no difference between postoperative morphine equivalent dose (MED) for plain bupivacaine versus LB (25.3 ± 65.8 vs. 24.9 ± 31.7 MED; $p = 0.159$) or length of hospital stay (15.8 ± 12.0 hours vs. 23.8 ± 20.0; $p = 0.094$). Furthermore, subjective pain was also similar between groups (0 vs. 1.6 ± 2.6, $p = 0.68$), (4.6 ± 2.3 vs. 4.9 ± 2.0 average POD 1 pain, $p = 0.534$) and (4.3 ± 2.1 for vs. 4.9 ± 2.1 average POD 2 pain, $p = 0.373$).*

Conclusion: *LB is not superior to plain bupivacaine for controlling pain following vaginal reconstructive surgery, and justification for the exponentially greater cost of LB is not supported. Prospective investigations with larger sample sizes are needed to determine the optimal pain management for levatorplasty in vaginal reconstructive surgery.*

Key Words: reconstructive surgical procedures, pelvic organ prolapse, postoperative pain, bupivacaine, local anesthesia, nerve block

Introduction

Liposomal bupivacaine (LB) is an encapsulated bupivacaine in multivesicular liposomes leading to increased stability and longer duration of drug release. Its duration of action is 72 hours compared to 2-9 hours for plain bupivacaine.[1] LB was FDA approved in 2011 after it was shown to result in decreased postoperative pain and opioid use following hemorrhoidectomy and bunionectomy.[2,3] Since its approval, it has also been found to improve postoperative recovery after breast augmentation, inguinal hernia repair and total knee replacement procedures.[4] Pudendal nerve blockade provides effective anesthesia to the vulva, posterior vagina and perineum, which are the typical locations patients complain of pain following vaginal reconstructive surgery.[5] Use of local anesthetic in vaginal surgery has been shown to have a beneficial effect on postoperative pain. However, pain control outcomes when utilizing LB have been mixed, and reviews of the available studies on the use of LB for infiltration of the surgical site and peripheral nerve blockade concluded the effectiveness of LB is unclear due to inconsistent results.[4,6] The cost of plain bupivacaine can vary based on the supplier, but is at least 100x less expensive than the same volume

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of LB. This significant cost difference highlights the need to clarify the benefit that this proprietary drug formulation imparts. The purpose of this study was to compare the efficacy of plain bupivacaine and LB for postoperative pain control in patients undergoing levatorplasty in vaginal reconstructive surgery. The primary outcomes were postoperative narcotic use and subjective pain score. The secondary outcome was length of hospital stay.

Material and methods:

This is a study that included women undergoing levatorplasty as part of surgical intervention for a rectocele and perineocele at a single institution between June 2016 and December 2021. During this period, patients who met inclusion criteria were randomly assigned to receive either LB or plain bupivacaine for local anesthesia at the time of their procedure. These patients were then retrospectively evaluated. This study was approved by the Institutional Review Board (IRB #5150320).

Female patients were eligible for inclusion if they were 18 years of age or older, English-speaking, not pregnant or nursing, and consented to a rectocele repair with levatorplasty. Patients were excluded if they had an allergy or contraindication to bupivacaine use, severe cardiovascular, hepatic or renal disease, neurologic impairment or a history of substance abuse.

Demographic data was assessed via chart review. Twenty-five patients received a pudendal nerve block with LB at the time of their procedure. In order to make a comparison, 25 clinically similar patients who had pudendal nerve block with plain bupivacaine during the same time period were selected. The plain bupivacaine was purchased by our facility for a price of $1.80 per 20 mL and the LB was purchased for $354.60 per 20 mL.

Baseline pain scores were calculated for each participant preoperatively on the day of surgery using a validated questionnaire (Brief Pain Inventory).[7] Levatorplasty was performed as an adjunct to the rectocele repair to increase pelvic floor support. This was accomplished with plication of the levator plate to the midline using absorbable Vicryl sutures. The pudendal nerve block was performed at completion of the procedure with a total of 20 mL of LB or 20 mL of 0.25% plain bupivacaine. The ischial spine was first palpated with the surgeon's index finger. The anesthetic (5 mL) was then injected near the ischial spine using a spinal needle pointing towards the ipsilateral shoulder, and the injection was continued while retracting the needle. This was repeated on the contralateral side. The final 10 mL was divided between the insertion of the levator plate on each side. The pudendal blocks were either performed or supervised by the same fellowship trained surgeon. Postoperatively, the patients were provided with a multimodal pain regimen including narcotic medication as needed.

Our primary outcomes were postoperative narcotic use and subjective pain scores. The total opioid consumption of each patient was quantified using the morphine equivalent dose, which was calculated retrospectively via chart review. Previously recorded postoperative day 1 and 2 pain scores obtained using a Brief Pain Inventory (BPI) form were compared. The average postoperative lengths of stay in hours were averaged and compared between the two groups.

The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Comparisons between two groups of non-normally distributed independent variables were analyzed using the Mann-Whitney U-test. T test was used for normally distributed variables. Categorical variables were compared using chi-square test. Descriptive statistics are presented as the mean ± standard deviation. P values < 0.05 were considered statistically significant.

Results

Mean age, body mass index, and Baden-Walker grade of posterior prolapse were comparable between groups, Table 1. The prevalence of neuropsychiatric diseases amongst participants, including chronic pelvic pain, chronic back pain, anxiety, and depression, were evaluated and did not differ significantly between groups, Table 1. There was no significant difference between groups in terms of education levels ($p = 0.115$).

Intraoperative estimated blood loss (96.0 ± 112 vs. 91.2 ± 56.1 mL, $p = 0.853$) was similar between both groups. No intraoperative complications were recorded for any of the surgeries. There was no significant difference in 30-day postoperative complication rates between the two groups, Table 2. Urinary tract infections were reported in four patients in the plain bupivacaine group versus five patients in the LB group. Additionally, one patient in the plain bupivacaine group was admitted for a transient ischemic attack. In the LB group, one patient was readmitted for nausea and vomiting, and another for incision and drainage of a suprapubic abscess. Eight patients in the plain bupivacaine group versus six in the LB group failed their postoperative voiding trials, Table 2.

TABLE 1. **Comparison of patient characteristics**

	Plain bupivacaine group (n = 25)	**Liposomal bupivacaine group (n = 25)**	**p value**
Mean age	62.8 ± 11.8	62.5 ± 12.6	0.927
Mean body mass index	27.8 ± 5.2	29.1 ± 6.2	0.426
Mean Baden-Walker grade posterior prolapse	2.3 ± 1.2	2.1 ± 1.1	0.651
Neuropsychiatric			
Chronic pelvic pain	8.7% (2)	24.0% (6)	0.155
Chronic back pain	10.5% (2)	8.3% (2)	0.431
Anxiety	24.0% (6)	12.0% (3)	0.269
Depression	24.0% (6)	24.0% (6)	1
Education level			0.115
High School education only	21.4% (3)	53.8% (7)	
College education only	35.7% (5)	7.7% (1)	
Graduate education and above	42.9% (6)	38.5% (5)	

Inpatient narcotic use was recorded for all participants and the total morphine equivalent dose (MED) was calculated. Postoperative MED was 25.3 ± 65.8 in the plain bupivacaine group compared to 24.9 ± 31.7 in the LB group (p = 0.159) during the hospitalization. Length of hospital stay was similar between groups (15.8 ± 12.0 and 23.8 ± 20.0 hours, respectively; p = 0.094). Furthermore, subjective worst and average pain scores were also similar between groups (worst pain: 6.6 ± 2.5 vs. 6.7 ± 2.3 p = 0.940 and average pain: 4.6 ± 2.2 vs. 4.9 ± 1.9, p = 0.534), Table 2.

TABLE 2. **Postoperative outcomes**

	Plain bupivacaine group (n = 25)	**Liposomal bupivacaine group (n = 25)**	**p value**
Preoperative pain (BPI)	0	1.6 ± 2.6	0.68
Postoperative length of stay (hours)	15.8 ± 12.0	23.8 ± 20.0	0.094
Morphine equivalent dose (in the hospital)	25.3 ± 65.8	24.9 ± 31.7	0.159
Postoperative worst pain (BPI)	6.6 ± 2.5	6.7 ± 2.3	0.940
Average pain POD 1 (BPI)	4.6 ± 2.3	4.9 ± 2.0	0.534
Average pain POD 2 (BPI)	4.3 ± 2.1	4.9 ± 2.1	0.373
Postoperative complications			
Urinary tract infection	16% (4)	20% (5)	0.713
Readmission	4% (1)	8%	0.552
Failed voiding trial	32% (8)	24% (6)	0.529

BPI = brief pain inventory; POD = postoperative day

Discussion

This study demonstrated no difference in the amount of postoperative opioid use or subjective pain scores between the plain bupivacaine and LB groups when utilized as a pudendal nerve block for patients undergoing levatorplasty during vaginal reconstructive surgery. There was also no significant difference in the length of postoperative hospital stay in our study. When comparing cost, the price difference was over 100 times greater for LB when compared to plain bupivacaine.

Liposomal bupivacaine has garnered significant interest due to its longer duration of action and potential to decrease postoperative narcotic use. However, several similar studies have failed to show a clinically significant difference in patient outcomes. Evans et al compared injection of LB versus normal saline in the posterior vaginal compartment and perineal body in women undergoing pelvic reconstructive procedures that included posterior colporrhaphy and perineorrhaphy.[8] There were no differences in the primary outcome of vaginal pain or secondary outcomes of narcotic use, time to first opioid, length of stay, return of bowel function or void trial success. Jones et al also compared LB to normal saline injected into the lateral vaginal wall/levator muscle area and perineal body in women undergoing posterior vaginal wall surgery.[9] Their results similarly failed to show a significant difference in the pain scores or morphine equivalent doses between the study and placebo groups. Yeung and colleagues also performed a placebo-controlled trial of LB in the laparoscopic and vaginal incisions of women undergoing robotic sacrocolpopexy with posterior repair.[10] They found equivalent postoperative pain scores and narcotic use between the experimental and control groups as well. While all of the aforementioned studies evaluated pain control following posterior vaginal wall reconstruction, none of them utilized LB for regional anesthesia.

To date, there are three systematic reviews that have examined the use of LB for peripheral nerve blockade in a variety of surgical procedures.[6,11,12] Each review included between four and thirteen studies. None of the included data was specific to pelvic or perineal surgery. Two of the three were unable to draw definitive conclusions due to mixed results. The third study did find statistically significant, but clinically unimportant improvement in postoperative pain scores. Notably, this benefit became insignificant after excluding the data from an industry-sponsored trial. An additional systematic review of the use of LB for surgical site infiltration also had inconclusive results.[4]

In contrast, there are several studies that did find statistically significant benefit to using LB. Mazloomdoost et al compared LB to placebo for pain control following retropubic midurethral sling (MUS) placement.[13] The group that received LB had lower postoperative pain scores and lower opioid consumption, though there was no difference in satisfaction scores. Iwanoff et al also utilized LB for retropubic MUS surgery, but instead compared it to plain bupivacaine mixed with lidocaine. The median pain scores for the LB group were lower, but there was no difference in opioid or NSAID consumption, so the benefit was considered not to be clinically significant. Barron and colleagues came to a similar conclusion when comparing LB to plain bupivacaine for laparoscopic or robotic abdominal hysterectomies.[14] Most recently, Dengler et al evaluated the use of LB for pain control following vaginal reconstructive procedures involving posterior colporrhaphy.[15] A pudendal nerve block was performed with plain bupivacaine versus plain bupivacaine mixed with LB. Their results demonstrated statistically significant improvement in postoperative pain scores, as well as lower ibuprofen and acetaminophen use in the patients who received LB. Other measured outcomes, including the total opioid consumption, remained equivalent between the two study groups.

While some of these studies were able to find statistically significant differences in the pain scores with the use of LB, none of them were able to show a decrease in postoperative narcotic use. Other outcomes, including patient satisfaction, time to return of bowel function and void trial success, were also not found to be significantly different when evaluated. These findings call into question the clinical benefit of using LB in this context. The advantage of using LB has been important to clarify due to the expense the product imparts on our healthcare system. The price of bupivacaine can vary based on the formulation and supplier. Currently, our hospital is able to purchase the product for 9 cents per mL, resulting in a cost of $1.80 for 20 mL, while others have quoted a price of approximately $3.00 per 20 mL. LB remains at least one hundred times more expensive with a price of $354.60 per 20 mL. Based on our findings, the increased cost of LB is not offset by improvements in other postoperative parameters.

The narcotic usage in each group was compared using the average morphine equivalent doses. Notably, this data included only the narcotics used prior to discharge. Due to variations in the amount of narcotic medication prescribed on discharge and the inherent inaccuracy in patient-reported narcotic use, total amounts of narcotics used postoperatively

were not assessed. Given the statistically similar postoperative lengths of stay between the two groups, this remains a helpful comparison. There is no indication that recording narcotic consumption for the extent of the study period would alter our results as the postoperative pain scores remained equivalent.

Postoperative complications rates were equivalent between the two study groups and comparable to those described in similar studies.[8,13,16] Adverse events related directly to pudendal nerve blockade or use of local anesthetic, such as hematomas, irritation at injection sites and local anesthetic toxicity, were not reported by our study participants. There was no significant difference in the percentage of patients in each group who failed their postoperative voiding trial. Most of these patients were managed with short term catheter replacement, though at least one patient was started on clean intermittent catheterization. The rate of postoperative urinary retention in our study is consistent with that previously documented following posterior colporrhaphy.[8,10,17] In general, postoperative urinary retention after a surgical pelvic floor reconstruction seems to be attributed to local and general anesthesia disrupting neural circuity.

The strengths of this study include the comparison of patients treated by a single surgeon, allowing optimal uniformity in surgical technique, as well as pudendal nerve block administration. Although postoperative pain scores and narcotic usage can be affected by preexisting mental health and chronic pain conditions, these patients were not excluded from the study as these conditions are prevalent in our patient population. The presence of chronic pain conditions was determined to be equivalent between the two study groups. The limitations of this study are the retrospective nature, small sample size and limited postoperative follow up, as well as absence of a placebo group.

Other potentially informative criteria that were not evaluated include patient satisfaction and non-narcotic analgesia use. Additional prospective studies are needed to better characterize the optimal solution for pain control following vaginal reconstructive procedures.

Conclusion

Liposomal bupivacaine is not superior to plain bupivacaine for controlling pain following vaginal reconstructive surgery. The significantly increased cost of LB was not offset by decreasing length of stay or decreased narcotic usage. Further research is needed to develop the optimal pain control solution for this patient population. □

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