Original Article

Liposomal bupivacaine reduces opioid requirements following Ravitch repair for pectus excavatum

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Abstract

Background and Aims: The management of post-operative pain after surgical repair of pectus excavatum with the Ravitch procedure is challenging. Although previous studies have compared various methods of pain control in these patients, few have compared different local anesthetics. This retrospective analysis compares the use of bupivacaine to its longer-acting form, liposomal bupivacaine, in patients who had undergone pectus excavatum repair with the Ravitch method.

Material and Methods: Eleven patients who received local infiltration with liposomal bupivacaine were matched to 11 patients who received local infiltration utilizing bupivacaine with epinephrine. The primary outcome was total morphine milligram equivalents per kilogram body weight (MME/kg) over the complete length of hospital stay. Secondary outcomes included total cumulative diazepam, acetaminophen, ondansetron, and NSAID dose per kilogram body weight (mg/kg) over the course of the hospital stay, chest tube drainage (ml/kg body weight), number of post-operative hours until the first bowel movement, Haller Index, patient request for magnesium hydroxide, average pain scores from post-operative day 1 to post-operative day 5, and length of hospital stay. Continuous variables were reported as medians with inter-quartile ranges, and categorical values were reported as percentages and frequencies.

Results: The total MME/kg [1.7 (1.2-2.4) vs 2.9 (2.0-3.9), P = 0.007] and hydromorphone (mg/kg) [0.1 (0.0-0.2) vs 0.3 (0.1-0.4), P = 0.006] use in the liposomal bupivacaine group versus bupivacaine with epinephrine was significantly reduced over total length of hospital stay. Similarly, there was a reduction in diazepam use in the liposomal bupivacaine group versus the bupivacaine group [0.4 (0.1-0.8) vs 0.6 (0.4-0.7), P = 0.249], but this did not reach statistical significance. The total dose of ondansetron (mg/kg) was not statistically different when comparing the liposomal bupivacaine group to the bupivacaine group [0.3 (0.0-0.5) vs 0.3 (0.2-0.6), P = 0.332]. Interestingly, the total dose of acetaminophen (mg/kg) was statistically increased in the liposomal bupivacaine group compared to the bupivacaine with epinephrine group [172 (138-183) vs 74 (55-111), P = 0.007]. Additionally, the total chest tube drainage (ml/kg) was significantly reduced in the liposomal bupivacaine group [9.3 (7.5-10.6) vs 12.8 (11.3-18.5), P = 0.027]. Finally, the percentage of patients without requests for magnesium hydroxide to promote laxation was significantly higher in the liposomal bupivacaine group than in the bupivacaine group (63.6% vs 18.2%, P = 0.027).

Conclusion: The use of liposomal bupivacaine for local infiltration in patients who undergo the Ravitch procedure for pectus repair offers advantages over plain bupivacaine, including reduced opioid consumption and opioid-related side effects. However, more data are needed to understand the significance of these findings.

Keywords: Liposomal bupivacaine, pectus excavatum, Ravitch procedure

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Introduction

Pectus excavatum is a congenital depression of the sternum and associated rib cartilages. The severity of pectus excavatum has classically been defined using the Haller Index, which is the ratio of the transverse diameter to the anteroposterior diameter of the chest at the point of the greatest chest wall deformity. A normal Haller index is between 2 and 3, with surgical repair typically considered for a ratio over 3.25.[1]

Surgical repair of pectus excavatum presents challenges for post-operative pain control. Various pain management regimens have been described, including intravenous patient-controlled analgesia (PCA) with opioids, intercostal nerve blocks, thoracic epidurals, and paravertebral blocks.[2-6] No single method, however, has proven to be superior. Although the incidence of complications is low with regional analgesic techniques, some complications, such as spinal cord injury and pneumothorax, carry high morbidity. Comparison of pain management regimens for pectus repair may be constrained by different surgical repair techniques, such as the classic Ravitch procedure, the modified Ravitch procedure, and the Nuss procedure, with further variations of each technique.[7]

Although local anesthetics provide effective analgesia, their effect is of a relatively short duration (6–10 hours). Liposomal bupivacaine utilizes technology that employs multi-vesicular liposomes containing bupivacaine, resulting in sustained release of bupivacaine into the tissue for 72 to 96 hours.[8,9] Many published studies demonstrate the efficacy of liposomal bupivacaine for a variety of surgical procedures; however, there are no studies on the use of liposomal bupivacaine for patients undergoing Ravitch repair.[10] We hypothesized that the use of liposomal bupivacaine could reduce the use of opioid-class pain medications.

Material and Methods

For several years, the institutional method of pain management for patients undergoing Ravitch repair at our hospital consisted of modified intercostal nerve blocks performed under direct visualization at the time of surgery in addition to local wound infiltration, both utilizing bupivacaine with epinephrine. In March 2018, liposomal bupivacaine was substituted for bupivacaine with epinephrine for our modified intercostal nerve blocks and wound infiltration, allowing for comparison of techniques.[10,11] Post-operative pain management was achieved with opioid (hydromorphone) PCA, ketorolac, ibuprofen, and oral acetaminophen. After discontinuation of PCA, patients received hydrocodone or oxycodone as needed (PRN) for pain. There was no change in the post-operative pain management protocol after the institution of liposomal bupivacaine for intercostal nerve blocks and local wound infiltration.

The primary outcome of the study was total opioid requirement in patients who received liposomal bupivacaine compared to patients who received conventional bupivacaine with epinephrine after Ravitch repair for pectus excavatum. Secondary outcomes included total doses of adjuvant medications, including diazepam, ondansetron, ketorolac, ibuprofen, and acetaminophen over the course of the hospital stay. Additional secondary outcomes included chest tube drainage, time to the first bowel movement, patient request for magnesium hydroxide ($MgOH_2$) to promote laxation, average pain scores from post-operative day 1 to post-operative day 5, and total length of hospital stay in hours.

This single-center, case-controlled observational study was reviewed by the Institutional Review Board (IRB) and was determined to be exempt and did not require patient or parental consent. All procedures were performed at one institution by two surgeons. Eleven patients undergoing Ravitch repair for pectus excavatum using liposomal bupivacaine infiltration between March 2018 and February 2020 (mean age 20.2 years, mean weight 60.8 kg) were age-, weight-, and gender-matched to 11 patients undergoing Ravitch repair using 0.25% bupivacaine with epinephrine infiltration between January 2017 and December 2018 (mean age 20.7 years, mean weight 61.5 kg). Data were obtained by retrospective analysis of each patient's electronic medical record (Cerner Corporation, North Kansas City, MO). Information recorded included total doses of opioids, ketorolac, acetaminophen, ibuprofen, diazepam, and ondansetron over the course of the hospital stay. All non-opioid medication doses are reported as total milligrams per kilogram body weight (mg/kg) for the duration of each patient's hospitalization. Opioid usage is reported as morphine milligram equivalents per kilogram body weight (MME/kg). Other data collected included wound drainage volume per kilogram body weight (ml/kg), Haller index, time to the first bowel movement after surgery, patient request for $MgOH_2$, average pain scores from post-operative day 1 to post-operative day 5, and average length of hospital stay in hours.

The dose of liposomal bupivacaine for wound infiltration, which was used off-label in the study population, was based on patient weight. Plain bupivacaine 0.5% was combined with liposomal bupivacaine in order to provide a more immediate local anesthetic benefit. The liposomal bupivacaine/plain bupivacaine solution was diluted to 50 mL using normal saline to ensure an adequate volume for injection at the sternal incision, the chest tube sites, and intercostal spaces.

The mixture was injected subdermally every 1–2 cm as per the manufacturer's recommendation. Surgeons were trained on the injection technique by the manufacturer.

Statistical analysis

Statistical analysis was performed using Statistical Analysis Software (SAS, version 9.4). All continuous variables were summarized as median and 25^{th} to 75^{th} percentiles [inter-quartile ranges (IQRs)]. These were compared by type of local anesthesia using Wilcoxon signed-rank test. The categorical variable (request for $MgOH_2$) was summarized as frequencies and percentages. These were compared by type of local anesthetic using McNemar's test.

Results

The two groups were well matched for age, weight, and gender [Table 1]. The Haller index was statistically lower for the liposomal bupivacaine group versus the bupivacaine group [3.8 (3.5-5.0) vs 6.1 (5.1-7.6), $P = 0.001$, Table 1]. The liposomal bupivacaine patients required significantly less MME/kg than the plain bupivacaine with epinephrine patients [1.7 (1.2-1.4) vs 2.9 (2.0-3.9), $P = 0.007$, Table 2]. There was a significant reduction in hydromorphone use (mg/kg) in the liposomal bupivacaine group [0.10 (0.0-0.2) vs 0.3 (0.1-0.4), $P = 0.006$, Table 2]. Although there was a reduction in the total diazepam dose in mg/kg [0.4 (0.1-0.8) vs 0.6 (0.4-0.7), $P = 0.24$, Table 2], this did not reach statistical significance. There was no significant difference in the use of ondansetron, ketorolac, or ibuprofen between the two groups [Table 2]. Acetaminophen use (mg/kg) was significantly higher in the liposomal bupivacaine group [156.1 vs 87.1, $P = 0.007$, Table 2]. Post-operative wound (chest tube) drainage (mL/kg) was significantly lower in the liposomal bupivacaine group than in the bupivacaine group [9.3 (7.5-10.6) vs 12.8 (11.3-18.5), $P < 0.027$, Table 3]. The time to the first bowel movement (hours) was not significantly different in the liposomal bupivacaine group versus the bupivacaine group [59 (52-92) vs 73 (51-83), $P = 0.64$, Table 3]. Four out of 11 patients in the liposomal bupivacaine group compared to nine out of 11 in the bupivacaine group requested $MgOH_2$. The percentage of patients without requests for $MgOH_2$ was significantly higher in the liposomal bupivacaine group than in the bupivacaine group [63.6% vs 18.2%, $P = 0.027$, Table 3]. The average pain scores on the day of surgery and for 4 post-operative days were not statistically different between the two groups [Table 4]. The average length of hospital stay (hours) in the liposomal bupivacaine group versus the bupivacaine group was also not statistically different [99 (97-118) vs 120 (97-124), $P = 0.231$, Table 4].

Table 1: Patient demographics

	(*n*=11)		*p**
	Liposomal Bupivacaine	Bupivacaine	
Age (years)	19 (15, 23)	17 (15, 23)	0.801
Weight (kg)	61 (57, 66)	61 (52, 70)	0.966
Height (m)	1.77 (1.63, 1.78)	1.70 (1.66, 1.78)	0.814
Haller Index	3.8 (3.5, 5.0)	6.1 (5.1, 7.6)	0.001
Sex: Female	4 (36.4%)	3 (27.3%)	0.564

Either median (IQR) or counts (%) * Either Wilcoxon signed-rank test or McNemar's Test

Table 2: Drug usage (mg/kg)

	(*n*=11)		*p**
	Liposomal Bupivacaine	Bupivacaine	
MME/kg	1.7 (1.2, 2.4)	2.9 (2.0, 3.9)	0.007
PCA	0.1 (0.0, 0.2)	0.3 (0.1, 0.4)	0.006
Diaz	0.4 (0.1, 0.8)	0.6 (0.4, 0.7)	0.249
Keto	3.8 (3.6, 4.2)	3.8 (3.4, 4.6)	0.654
Ibup	51 (12, 79)	26 (0, 57)	0.465
Acet	172 (138, 183)	74 (54, 111)	0.007
Ondan	0.3 (0.0, 0.5)	0.3 (0.2, 0.6)	0.322
Median (IQR)			

** Wilcoxon signed-rank test. All drug values are the total doses of the drug during the entire hospitalization MME/kg=morphine equivalent/kg PCA=hydromorphone PCA dose Diaz=diazepam Keto=ketorolac Ibup=ibuprofen Acet=acetaminophen Ondan=ondansetron*

Table 3: Chest tube drainage, time to the first bowel movement, and patient request for magnesium hydroxide ($MgOH_2$)

	(*n*=11)		*p**
	Liposomal Bupivacaine	Bupivacaine	
Wound Drainage (ml/kg)	9.3 (7.5, 10.6)	12.8 (11.3, 18.5)	0.027
First Bowel Movement (hours)	59 (52, 92)	73 (51, 83)	0.637
Patient Request for $MgOH_2$			
Yes	4 (36.4%)	9 (81.8%)	
No	7 (63.6%)	2 (18.2%)	0.025

*Either median (IQR) or counts (%) * Either Wilcoxon signed-rank test or McNemar's Test*

Discussion

Current trends in surgical pain management involve various opioid-sparing methods, including regional anesthesia, local anesthetic wound infiltration, and non-opioid adjuncts. Although opioids are potent analgesics, they are associated with a number of undesirable non-analgesic side effects including sedation, respiratory depression, nausea, emesis, urinary retention, constipation, tolerance, and physical dependence.[12] Ready availability and liberal use of opioids have contributed to the current epidemic of opioid misuse.[13] Opioid tolerance and opioid-induced hyperalgesia can also have negative effects on surgical outcome.[14] The post-operative pain management

Table 4: Comparative Pain Scores (PS) and Length of Hospital Stay (LOS)

	(*n*=11)		*p**
	Liposomal Bupivacaine	Bupivacaine	
PS Day 1	3.1 (2.1, 4.0)	3.8 (2.6, 4.5)	0.193
PS Day 2	3.6 (2.9, 4.1)	2.9 (1.9, 3.8)	0.071
PS Day 3	2.8 (2.0, 3.7)	2.8 (1.3, 4.1)	0.715
PS Day 4	2.7 (2.2, 3.5)	2.0 (1.5, 4.3)	0.688
PS Day 5	1.8 (1.6, 4.0)	2.2 (1.7, 3.5)	0.445
Length of Stay (Hours)	99 (97, 118)	120 (97, 124)	0.231

*Median (IQR) * Wilcoxon signed-rank test*

of pectus excavatum repair with the Ravitch procedure has remained relatively unchanged over many years at our hospital, with the exception of the introduction of liposomal bupivacaine. This consistency, along with the standard use of opioids and benzodiazepines, made the Ravitch population ideal for pre- and post-liposomal bupivacaine comparison.

When compared to wound infiltration using bupivacaine with epinephrine, our study shows that wound infiltration using liposomal bupivacaine reduces the need for opioids during hospitalization in patients undergoing Ravitch repair for pectus excavatum. Although average pain scores were not statistically different between the two groups [Table 4], the reduction in opioid use suggests improved pain management over the patient's entire post-operative course.[15] Pain scores are a more accurate reflection of pain at specific times rather than over the course of a hospitalization. There was an increased use of acetaminophen in the liposomal bupivacaine group that may have contributed to the reduced use of opioids.[16] Although this is certainly a confounding variable, it may be possible that patients in the liposomal bupivacaine group had less severe pain and were thus treated with acetaminophen rather than with an opioid. Further delineation would require a prospective study with adherence to a standardized pain protocol.

The use of as-needed diazepam for muscle spasm was also reduced in the liposomal bupivacaine group, although this difference did not achieve statistical significance. The use of ondansetron was not significantly different between the two groups. The study may have been under-powered to detect the effect on diazepam and ondansetron use.

Constipation is a significant side effect of opioids. The time to the first post-operative bowel movement was not significantly different between the two groups. However, the percentage of patients not requesting $MgOH_2$ was significantly higher in the liposomal bupivacaine group versus the bupivacaine group. This suggests that patients in the liposomal bupivacaine group experienced less opioid-related constipation and therefore required less laxative medication.

An unexpected finding was the statistically significant difference in wound drainage output after surgery. Anecdotally, patients in the liposomal bupivacaine group appeared to ambulate earlier. Quantitatively documenting this was difficult and represents a limitation of this study. Earlier ambulation may promote better fluid drainage in the early post-operative period and earlier removal of chest tubes. Overall, this could lead to earlier hospital discharge and decreased hospital costs. Tracking this in a future prospective study would be informative.

The Haller index was statistically lower for the liposomal bupivacaine group versus the bupivacaine group. It is possible that a lower Haller index is indicative of less surgical dissection, thereby creating less wound drainage; however, the Haller index is a static measurement that reflects chest asymmetry and does not correlate well with patient symptoms or cardiopulmonary dysfunction and therefore may not correlate with the extent of surgical dissection or operative time.[1,17,18]

This study is limited by its single-institution, non-randomized, unblinded nature. Despite these limitations, our findings suggest that a future prospective study on the efficacy of liposomal bupivacaine for Ravitch may be worthwhile.

In conclusion, the use of liposomal bupivacaine for surgical wound infiltration in conjunction with multi-modal pain management reduces post-operative opioid use in patients undergoing Ravitch repair for pectus excavatum.

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Conflicts of interest

There are no conflicts of interest.

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