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Original Research

Liposomal bupivacaine reduces narcotic use and time to flatus in a retrospective cohort of patients who underwent laparotomy☆

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ABSTRACT

Introduction: Sustained release liposomal bupivacaine (LB) is a new pain control option that can reduce opioid use after laparotomy, which is known to prolong ileus, length of stay.

Methods: Sixty-one consecutive patients undergoing laparotomy were treated with a standardized multi-modal therapy (MMT) consisting of IV tylenol, toradol, and morphine/dilaudid PCA. Thirty-one of those patients were additionally treated with LB infiltrated during fascial closure. Endpoints were opioid use, time to flatus, length of stay, and complications.

Results: Overall opioid use for 72 h was 78 mg of morphine for the MMT + LB group and 112 mg in the MMT control group ($p = 0.04$). During 0–24 h s PCA use was similar. However, during 24–48 h PCA use was decreased by 46% in the MMT + LB group ($p = 0.038$), and decreased by 55% during the 48–72 h period ($p = 0.019$). Time to flatus was decreased by 1.0 days in the MMT + LB group ($p = 0.005$).

Conclusion: Use of LB in laparotomy patients decreases opioid use, time to flatus, and should be considered as a component of post-operative pain control.

1. Introduction

Over the last several decades, the healthcare community has made substantial progress in postoperative pain management due to consensus recommendations from professional societies and governmental agencies [1–3]. These recommendations endorse the use of multimodal techniques for pain control through the administration of two or more medications with different mechanisms of action. Despite the multimodal approach to pain relief, the majority of surgical patients still report a high incidence and severity of pain in the postoperative period [4,5].

Opioid analgesics are the foundation of medication regimens for pain control in the postoperative setting due to their documented efficacy in the treatment of moderate to severe pain [1,6]. Although highly efficacious, opioid analgesics are commonly associated with several opioid-related adverse events (ORAEs) including nausea, vomiting, constipation, dizziness, hypotension, sedation and respiratory depression [7]. A study by Apfelbaum and colleagues indicates that within two weeks following a completed surgery, 23% of the study population (n = 222) self reported at least one ORAE [4]. A separate study by Oderda and colleagues found that the overall rate of post-operative ORAEs in a national hospital database was 12.2% (n = 319,898). In the Oderda study, ORAEs were found to contribute to increased hospital length of stay and increased overall hospitalization costs [8]. Due to the serious nature of ORAEs, The Joint Commission issued a sentinel event alert concerning the safe use of opioids in the hospital setting. The alert identifies postsurgical patients as being at higher risk for over sedation and respiratory depression when treated with opioid analgesics [7]. Additionally, other studies have shown that patients undergoing gastrointestinal surgery are at an increased risk of experiencing ORAEs affecting gastrointestinal motility, nausea and vomiting [8,9].

Postoperative pain control remains a particularly relevant issue in patients undergoing laparotomy, and due to the morbidity and costs associated with ORAEs, researchers have aimed to find alternative opioid-sparing approaches to postoperative pain control [10–13]. Several of these studies employed the use of local anesthetics and were able to document analgesic efficacy and reduced opioid requirements in the immediate postoperative period [11,12]. However, local anesthetics have a short duration of action with the maximum therapeutic window for bupivacaine infiltration lasting 4–8 h [14,15]. Continuous long-term

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administration of local anesthetics has been achieved but requires the use of costly subcutaneous pumps to attain the necessary duration of pain control [11,12]. Liposome bupivacaine (LB) offers a unique solution to this issue, as it provides a slow release of the local anesthetic bupivacaine into the surgical site to produce sustained postsurgical anesthesia [16]. Liposome bupivacaine employs a depofoam technology that has been shown to release the medication over an extended period of 72 h and thus lengthen the time that each patient's pain is controlled [16]. Liposomal bupivacaine has been shown to be effective at reducing post-operative pain for hemorrhoidectomy [17], laparoscopic abdominal surgery [18], and small incision operations like umbilical hernia repair [19]. Liposomal bupivacaine has also shown efficacy as part of an overall non-opioid multimodal regimen to improve pain control in ileostomy reversal [20,21]. These multimodal regimens, which include liposome bupivacaine, have also proven to significantly reduce post-surgical opioid consumption, hospital length of stay, and hospitalization costs when compared with a purely opioid-based standard of care therapy [18,22]. However, no studies to date have examined the isolated benefit of LB alone when added to a multi-modal therapy (MMT) regimen as the standard of care in laparotomy patients. Therefore, our objective was to determine the effect of intra-operative LB injection on post surgical opioid use and pain control in patients undergoing laparotomy.

2. Methods

Study design was a single center retrospective review of a prospectively collected database. Eligibility criteria were broad and included patients > 18 years, undergoing elective laparotomy (midline and subcostal incisions) for malignancy from December 2013 to December 2014, at a University Hospital, by a single surgeon. Pregnant patients and those with an epidural were excluded. Liposomal bupivacaine (LB) use was introduced into the surgical oncology practice at this institution in April 2014. Our control group consisted of 30 consecutive laparotomy patients prior to the introduction of LB whose post-operative pain control was a standard multimodal therapy (MMT). Our MMT regimen was a standardized regimen where every patient received 1) scheduled IV Tylenol 1000 mg every 8 h for 24 h beginning immediately post op, and 2) scheduled IV toradol 15 mg every 6 h for 24 h beginning on post operative day 1 if hemoglobin and creatinine were stable, and 3) morphine or dilaudid PCA begining immediately post op. Dilaudid PCA mg delivered were converted to morphine equivalents for standardization and comparison. Our test group consisted of cohort of 31 consecutive laparotomy patients who received their operations after we began regular use of LB as part of our standard of care. Each patient in the second group received a single standardized dose (266mg/20 ml) of intraoperative of LB in addition to the standard MMT regimen. This dose of LB was diluted to a standardized volume of 40 ml using sterile saline. Injection technique was standardized and performed in an identical manner in all cases. Immediately after fascial closure but prior to skin closure, LB was injected in a field block pattern divided evenly between either side of the incision. Fifty percent by volume was delivered into the anterior rectus fascial plane which was achieved by directly observing the fascia while skin was open making ultrasound visualization unnecessary. The remaining 50% was delivered into the subcutaneous tissue just deep to the dermis, also delivered by direct visualization prior to ski closure. The electronic medical record was used to determine our primary endpoints of 1) milligrams of morphine (or dilaudid morphine equivalents) delivered by PCA, 2) pain scores, 3) time to flatus, and 4) length of stay. We also measured adverse ORAEs and wound infections rates as additional endpoints. This study was IRB approved, and registered with www.researchregistry.com. This work has been reported in line with the STROCSS criteria [23]. There was no financial support of the study by the manufacturer.

Descriptive data analysis was performed as follows: continuous random variables were summarized as mean (SD) or median (interquartile range) depending on whether the data came from the normal distribution, an assumption that was validated by the Shapiro-Wilk test. Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between patients that received MMT and patients who received MMT + LB were examined using a two-sided *t*-test or Wilcoxon rank sum test, as appropriate. Comparisons of categorical variables were conducted using Fisher's exact test or Pearson's Chi-square test, as appropriate. Time-to-events variables, length of stay and time to flatus, were summarized by medians estimated by the Kaplan-Meier product limit method. Comparisons of time-to-event variables were performed using a two-sided log-rank test. Any $p < 0.05$ was considered statistically significant. All study data entered in a Microsoft Excel Office (Microsoft Corporation, Redmond, WA, USA) database was imported in to SAS version 9.4. All data analysis was performed using SAS 9.4 (SAS Institute Inc., NC, USA). Power calculations done using http://powerandsamplesize.com.

3. Results

Sixty one patients underwent laparotomy consecutively with the first 30 receiving MMT and the last 31 receiving MMT + LB for post-operative pain control. Study demographics are listed in Table 1. Both groups had similar age, gender distribution, incision type and length, type of PCA, and MMT administration (Table 1).

During the first 24 h, post-operative opioid use was similar between both groups (Fig. 1A). However, the MMT + LB group had a 46% reduction in opioid use during the 24–48 h period, and a 55% reduction in opioid use during the 48–72 h time period, which were both statistically significant (Fig. 1A). For the entire 0–72 h post operative period, the MMT + LB group had an overall reduction in opioid use of 30% that was statistically significant ($p = 0.04$ Fig. 1B).

Despite having a reduction in opioid use by PCA, both groups had similar post-operative pain scores in each of the time periods (Fig. 2A) and overall (Fig. 2B). Furthermore, rates of both wound infections and ORAE's were equivalent in both groups (Table 2).

With the large reduction in opioid use, the MMT + LB group also experienced a statistically significant reduction in the time to flatus. Median time to flatus was 3 days in MMT + LB group compared with 4

Table 1
Characteristics of patients treated with or without liposomal bupivacaine (LB).

Characteristics		MMT (n = 30)	MMT + LB (n = 31)	P-Value
Age	Mean (SD), years	62.8 (14.6)	65.1 (15.2)	0.5537
	Min - Max, years	32.2–89.4	29.3–91.5	
No. Female Patients	n (%)	9 (30.0)	16 (48.4)	0.0862
Incision Type				0.1976
Lower midline	n (%)	5 (16.7)	9 (29.0)	
Upper midline	n (%)	14 (46.7)	11 (35.5)	
Full midline	n (%)	4 (13.3)	0 (0.0)	
Subcostal	n (%)	5 (16.7)	8 (25.8)	
Other	n (%)	2 (6.7)	3 (9.7)	
Incision Length	Median (IQR), cm	14.0 (13.0–16.0)	14.0 (13.0–16.0)	0.9767
	Min - Max, cm	10.0–30.0	8.0–30.0	
Morphine/Dilaudid				
Morphine	n (%)	1 (3.3)	3 (9.7)	0.6124
Dilaudid	n (%)	29 (96.7)	28 (90.3)	
IV Tylenol within 24 h				
Not Administered	n (%)	6 (20.0)	4 (12.9)	0.5077
Administered	n (%)	24 (80.0)	27 (87.1)	
Toradol in first 48 h				
Not Administered	n (%)	3 (10.0)	3 (9.7)	1.0000
Administered	n (%)	27 (90.0)	28 (90.3)	

SD, standard deviation; IQR, interquartile range: 25th - 75th percentile.