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Research Article

Retrospective Study of Liposomal Bupivacaine for Pectus Excavatum Repair

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Abstract

Aim: The aim of this study is to assess whether Exparel (bupivacaine liposome injectable suspension, Pacira BioSiences, Inc., Parsippany, NJ) is superior to plain bupivacaine. Objectives: The objective of the study is to ascertain retrospectively whether Exparel use in patients undergoing surgical correction of pectus excavatum is effective in providing post-operative analgesia when compared to plain bupivacaine. **Methods:** 72 pediatric patients (36 in each group) undergoing surgical repair of pectus excavatum were included in this study. There were 36 patients in the liposomal bupivacaine (LB) group and 36 patients in the plain bupivacaine group. We compared the two groups for Morphine equivalent usage, adjuvant analgesic usage, pain scores, and length of stay. **Results:** The group that received the liposomal bupivacaine had lower morphine equivalent usage (1.75 mg/kg vs. 4.13 mg/kg, p-value=0.002), lower pain scores after 24 hours (p-value<0.001) and shorter length of stay (2.54 days vs 3.54 days, p-value=0.00002) compared to the group that just received plain bupivacaine. The total amount of bupivacaine did vary between groups (2.0 mg/kg vs. 1.4 mg/kg, p<0.001) as did the total volume of injectate (1.13 mL/kg vs. 0.33 mL/mg, p=0.008). No other variables were different. **Conclusions:** Liposomal bupivacaine appeared superior to bupivacaine hydrochloride for providing post-operative analgesia for patients undergoing pectus bar repair.

Keywords: Liposomal bupivacaine; Pectus excavatum; Post-operative pain; Analgesia; Local anesthetic

Introduction

Liposomal bupivacaine (LB) was approved for use in the United States on October 28, 2011. The bupivacaine, an amide type local anesthetic, is contained in multivesicular liposomes (MVL) in various sizes ranging from 24 to 31 mm in diameter. After injection the bupivacaine gradually elutes out from the MVL over a period of time. The FDA approved indications are for local infiltration and interscalene nerve blocks to produce postsurgical analgesia [1]. Analgesia can be prolonged and last up to 72 hours [2]. On March 22, the company announced that the US Food and Drug Administration had approved its supplemental new drug application to include the use in patients six years of age and older [3].

Pain after pectus procedures can be substantial and result in increased morbidity and length of stay [4]. Typical management of postoperative pain has historically been with opioid analgesics such as morphine sulfate. The deleterious side effects accompanying opioid use include respiratory depression, pruritis, nausea, vomiting, peripheral vasodilatation, and decreased gastrointestinal

motility. All can produce poor outcomes, including prolonged hospital stays, and higher costs [5]. Enhanced postoperative pain control has numerous benefits [6,7]. In acknowledgement of the need for more effective pain management, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) developed standards for the evaluation and treatment of pain in accredited hospitals and other health care facilities [8].

Multi-modal analgesia, the combination of different analgesic techniques, has demonstrated greater efficacy compared to any single method alone. Trials where regional techniques are combined with systemic analgesics have resulted in superior patient outcomes, including decreased lengths of stay [9]. The use of a continuous infusion of a long-acting local anesthetic at the operative site in the pediatric population has resulted in enhanced outcomes in several trials. Safety with the use of continuous wound infiltration with local anesthetics has also been demonstrated [10]. Local anesthetic infiltration has been demonstrated to decrease postoperative pain and discomfort in pediatric patients and speed the return to normal activities [11]. Moreover, Tirotta et al demonstrated that the continuous local infusion of bupivacaine, with an elastomeric pump, into the median sternotomy wound reduced opioid requirements in postsurgical pediatric cardiac patients [12].

Many different regional techniques have been employed to mitigate the pain after pectus procedures. Thoracic epidural analgesia is the standard of care in many hospitals [13-15]. Paravertebral blocks (PVB) are another modality [16] frequently used along with intercostal nerve blocks [17,18]. More recently, some new blocks have been used, like bilateral parasternal blocks [19] and fascial plane blocks like pectoralis blocks (PECS 1 and PECS 2) [20,21]. This study demonstrates the use of a new drug that can be used in most of these regional techniques and that obviates the need for catheters or redosing.

Methods

This study received Institutional Review Board Exempt status by the Research Institute of Nicklaus Children's Hospital.

Our institution began using LB in pediatric surgery patients in August 2017. For this retrospective study, all patients presenting for minimally invasive surgical repair of pectus excavatum (Nuss procedure) at Nicklaus Children's Hospital treated with LB between October 2017 and February 2021 were included in the study. This group was compared to a control pectus group prior to the LB era (pre-LB) which encompassed dates from July 2015 to September 2017, when bupivacaine HCl alone was used instead for post-operative analgesia.

We analyzed all pediatric patients undergoing surgical repair of pectus excavatum who were treated with LB. There were no exclusion criteria. Patients received 4 mg/kg of LB admixed with 0.25% bupivacaine in the following ratio: 3 mL bupivacaine for every 1 mL of LB. This was then diluted with 0.9% NS so there was enough volume to inject 10 mL/linear inch of incision and each intercostal nerve block. During the pre-LB era patients were treated with either 0.25% or 0.5% bupivacaine undiluted, with the concentration at the discretion of the surgeon. Patients in both groups received a combination of bilateral intercostal nerve blocks plus local infiltration by the surgeons, i.e., the injection technique was the same.

Demographic data was collected, as well as the use of adjuvant analgesics, pain scores, and hospital length of stay (LOS). The analgesics recorded included morphine (mg/kg), hydromorphone (mg/kg), fentanyl (mcg/kg), midazolam (mg/kg), acetaminophen (mg/kg), ketorolac (mg/kg), and dexmedetomidine (mcg/kg). We also analyzed pain scores recorded by the nursing staff. These scores were generally collected hourly. Pain scores were recorded in the numeric rating scale (NRS) and the Face, Legs, Activity, Cry and Consolability (FLACC) for both groups. The groups were followed for 96 hours or until hospital discharge, whichever came first.

Statistical methods

The mean and standard deviations were used to describe the sample and histograms used to visualize the results. A t-test was used to test the difference between the number of hospitalized days between the two groups. A t-test was also used for the total morphine milligram equivalents (MME) for the preLB and LB groups. An Area Under the Curve (AUC) was calculated for each patient using the NRS pain scale and another AUC using the FLACC pain scale. A multivariate t-test and Wilcoxon test were done for each of the four outcomes (NRS and FLACC for first 24 hours and then NRS and FLACC for the whole 96 hours) and then a Hottelling's T was done to test both the NRS AUC and the FLACC AUC together testing the differences between preLB and LB at 24 hours and then for all hours.

Results

Overall, there seventy-two patients in this study, thirty-six in each group. There was no significant difference in the demographic parameters between groups (Table 1). For the PreLB group 11 patients received 0.25% bupivacaine and 25 patients received 0.5% bupivacaine; we analyzed these as one group. All patients received their narcotics in the postoperative period via Patient Controlled Analgesia (PCA); it was morphine in the LB group and hydromorphone in the Pre LB group.

	LB	LB	PreLB	PreLB
	Mean	**SD**	**Mean**	**SD**
Age (years)	15.9	2.7	15.5	2.3
Weight (kg)	56	11.8	56.3	10.3
Height (cm)	173.4	8.7	170.2	8.8
cm-centimeters, kg-kilogram, SD-standard deviation				

Table 1: Demographics.

The t-tests for total MME (1.75 mg/kg vs. 4.13 mg/kg, p-value=0.002) and LOS (2.54 days vs 3.54 days, p-value=0.00002) and were significant (Tables 2 and 3). The LB group had a lower LOS and lower use of MME. There was no statistically significant difference in the use of any other analgesic between the groups, except the MME. These include acetaminophen, ibuprofen and ketoralac.

	LB	preLB
Mean	1.75	4.13
Variance	1.8	16.55
Observations	35	35
Hypothesized Mean Difference	0	
df	41	
t Stat	3.29	
P (T<=t) one-tail	0.001	
t Critical one-tail	1.68	
P (T<=t) two-tail	0.002	
t Critical two-tail	2.02	
t-Test: Two-Sample Assuming Unequal Variances		

Table 2: Total MME (mg/kg).

	LB	preLB
Mean	2.54	3.54
Variance	0.43	0.84
Observations	35	35
Hypothesized Mean Difference	0	
df	62	
t Stat	-5.24	
P (T<=t) one-tail	.000001	
t Critical one-tail	1.67	
P (T<=t) two-tail	.00002	
t Critical two-tail	2.00	
t-Test: Two-Sample Assuming Unequal Variances		

Table 3: LOS (days).

The individual outcomes for the FLACC 24-hour scores t-test were p=0.5395, Wilcoxon p=0.4433. The individual outcomes for the FLACC 96-hour scores t-test were p= 0.1863, Wilcoxon p= 0.0066. The individual outcomes for the NRS 24-hour t-test were p= 0.11, Wilcoxon p= 0.195); the individual outcomes for the NRS 96-hour t-test were p= 0.00027, Wilcoxon p= 0.0001962.

The Hotelling's t-test for 24-hour differences in NRS AUC and FLACC AUC was not statistically significant (p-value=0.125), but the Hotelling's t-test for 96 hours NRS AUC and FLACC AUC was statistically significant (p-value<0.001). So, the 24-hour pain score AUC was not statistically significant, but the 96-hour AUC was significant (Figure 1 and 2).

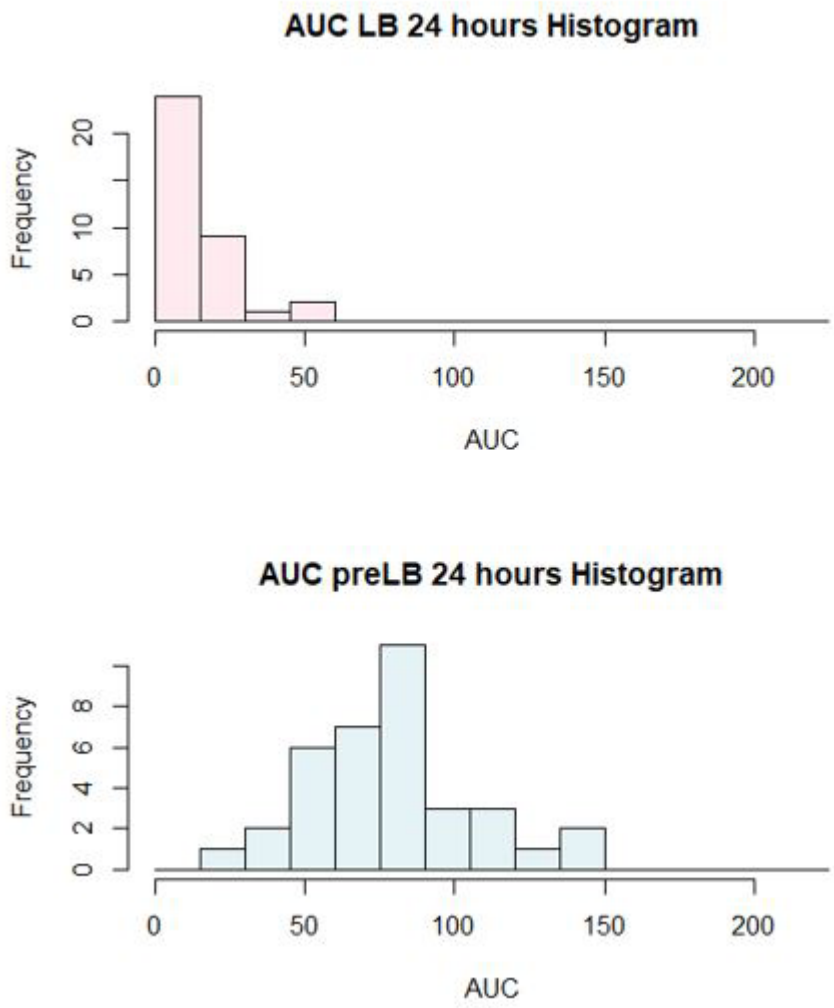

Figure 1: Pain Score Histograms, first 24 hours. AUC=area under curve; p-value = 0.125

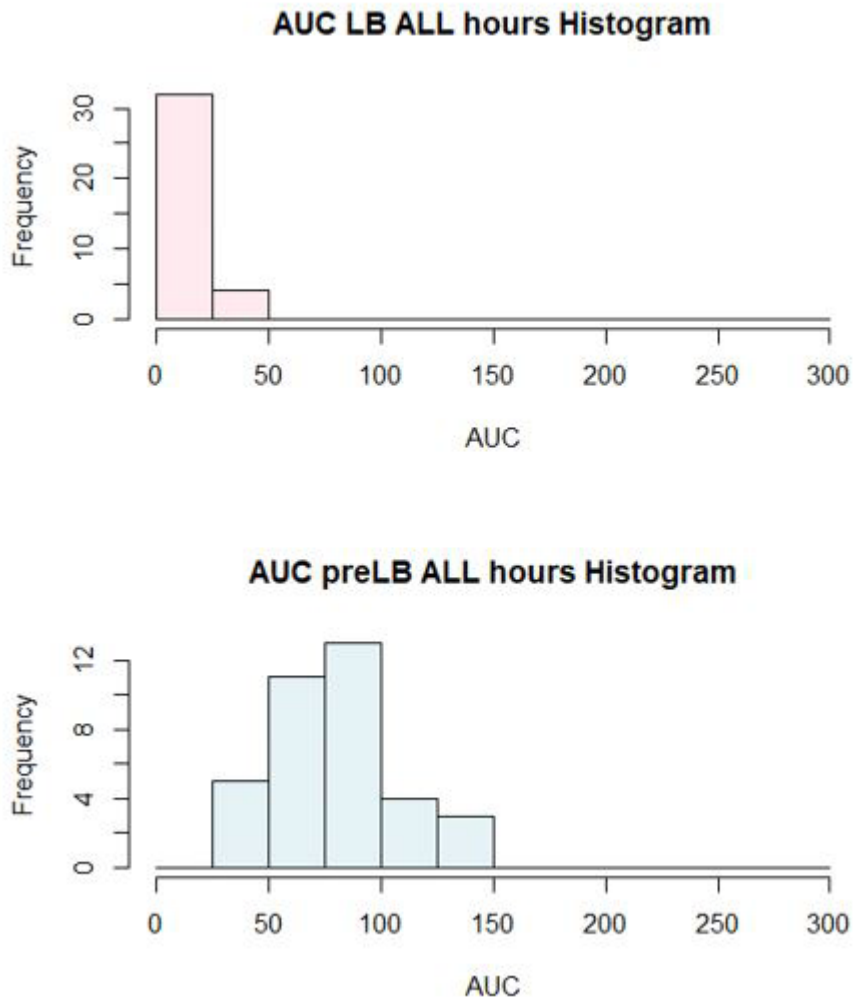

Figure 2: Pain Score Histograms All Hours. AUC=area under curve; p-value = 0.00034

The total amount of bupivacaine did vary between groups (2.0 mg/kg vs. 1.4 mg/kg, p<0.001) as did the total volume of injectate (1.13 mL/kg vs. 0.33 mL/mg, p=0.008).

Discussion

LB appeared to be superior to bupivacaine HCl for providing post-operative analgesia for patients undergoing pectus bar repair. The LB group required less MME, had lower pain scores after 24 hours and had a shorter LOS. This corroborates with a similar retrospective study in adults using LB for pectus surgery [22].

However, some caveats need to be addressed when evaluating these results. First, the data is retrospective; further prospective studies need to be completed to confirm these results. The amount of bupivacaine was also greater in the LB group. These factors alone could have affected the result. Second, subtle changes in patient management with non-opioid analgesics, like IV acetaminophen could have affected the results. Third, the sample size of 36 patients in each group is small, further limiting definitive conclusions.

Most importantly, the volume of the injectate differed between the groups as did the total amount of bupivacaine; both were greater in the LB group. The greater volume in the LB group is due to the lessor diffusion of the LB mixture compared to plain bupivacaine, requiring a greater volume to achieve the same degree of nerve blockade [23]. Secondly, it is known that there is a dose dependent

relationship with respect to duration of action with bupivacaine [24], with higher doses prolonging spinal blocks by a factor of 30 minutes or 50%, not orders or magnitude more [25,26] as was demonstrated in this study.

LB has demonstrated superiority to bupivacaine HCl for post-surgical analgesia, with comparable adverse effects. Dasta et al., reported a decrease in cumulative pain scores at 72 hours and a decrease in the use of morphine in a meta-analysis of nine prospective, double-blind, randomized controlled trials comparing liposomal bupivacaine to bupivacaine HCl [27]. The procedures included total knee arthroplasty, breast augmentation, inguinal hernia repair, bunionectomy and hemorrhoidectomy. Rice et al., demonstrated comparable analgesia in adult patients between posterior intercostal nerve block with LB and thoracic epidural analgesia after thoracotomy [28]. Many other studies have demonstrated similar results [29-31]. However, a recently published meta-analysis did not demonstrate any difference for perineural LB compared to plain bupivacaine [32]. This corroborated with a previous meta-analysis from 2017 which demonstrated the same finding [33]. Moreover, a recently published comprehensive summary of all randomized controlled trials (n=76) did not demonstrate any significant advantage of LB compared to other long-acting local anesthetics [34].

In a study contrasting the direct wound injection of LB at doses of 9, 18, and 30 mg/kg with plain bupivacaine at 9 mg/kg in dogs and rabbits, the peak plasma concentration after LB (C_{max}) was dose dependent, but significantly less than the level after plain bupivacaine. Moreover, the duration to peak plasma concentration was also significantly longer for liposomal bupivacaine [35]. The same investigators achieved similar results after peripheral nerve blocks [36]. In a human volunteer pharmacokinetic study comparing a subcutaneous injection of 20 mL of 2% LB with 20 mL of plain bupivacaine, 0.5%, no difference was found in the C_{max} despite the liposomal group getting four times the bupivacaine dose. More recently, a multicenter study to evaluate pharmacokinetics and safety of LB in pediatric patients aged 6 to 17 years (PLAY) demonstrated plasma bupivacaine levels well below the toxic threshold [37]. Furthermore, there was no difference in the incidence in adverse events with LB compared to the plain bupivacaine group.

There have been numerous retrospective studies suggesting efficacy in the pediatric population. Tirotta et al., demonstrated efficacy in pediatric cardiac surgery patients undergoing median sternotomy. This study compared patients who received an ON-Q® Pain Buster infusing bupivacaine into the wound to those receiving LB [38]. Day et al. showed effectiveness and safety in pediatric patients less than 15 years old undergoing pharyngoplasty [39]. The study by Hursey et al., also provided similar findings in older patients undergoing major surgeries for burn injuries. The results in all showed the LB groups received less opioids, had lower pain scores and lessor hospital stays compared with standard care using bupivacaine. Moreover, another study demonstrated efficacy and safety in pediatric spine patients when used with a multimodal pain management protocol [40].

The present study is one additional manuscript that adds to the compendium in pediatric patients. Further prospective trials should be conducted.

Conclusions

Liposomal bupivacaine appeared superior to bupivacaine hydrochloride for providing post-operative analgesia for patients undergoing pectus bar repair.

Ethical guidelines

This study received Institutional Review Board Exempt status by the Research Institute of Nicklaus Children's Hospital. The authors adhered to all ethical guidelines pertaining to retrospective studies and manuscript preparation.

Conflict of interest

Christopher F Tirotta, the corresponding author performs consulting work for Pacira BioSciences New Jersey, USA.

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