Retrospective Analysis

Liposomal Bupivacaine Versus Bupivacaine for Intercostal Nerve Blocks in Thoracic Surgery: A Retrospective Analysis

Kinjal M. Patel, MD[1], Noud van Helmond, MD[1], George M. Kilzi, MD[2], Akhil Patel MD[1], Frank W. Bowen, MD[3], David D. Shersher, MD[3], Keyur Trivedi, MD[1], and Ronak G. Desai, DO[1]

From: [1]Department of Anesthesiology, Cooper Medical School of Rowan University, Cooper University Hospital, Camden, New Jersey; [2]Cooper Medical School of Rowan University, Camden, New Jersey; [3]Department of Surgery, Cooper Medical School of Rowan University, Cooper University Hospital, Camden, New Jersey

Address Correspondence:
Kinjal M. Patel, MD
Department of Anesthesiology, Cooper Medical School of Rowan University
Cooper University Hospital
1 Cooper Plaza, 2nd Floor
Dorrance Bldg Suite# D206
Camden, NJ 08103
E-mail: Patel-Kinjal@cooperhealth.edu

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Background: Liposomal bupivacaine (LipoB), delivered via intercostal nerve blocks (ICNBs), is increasingly being used for postoperative pain control in thoracic surgery patients, but there is limited data on its effectiveness when compared to standard bupivacaine.

Objective: We sought to compare postoperative opioid use, pain control, and length of stay (LOS) in patients undergoing thoracic surgery with LipoB ICNBs vs patients undergoing thoracic surgery with ICNBs using standard bupivacaine.

Study Design: A retrospective analysis.

Setting: Research took place in a tertiary academic medical center.

Methods: A transition in the standard of care from standard bupivacaine to LipoB for ICNBs in March of 2014 allowed us to compare 2 cohorts: patients who received bupivacaine ICNBs from January 2013 through February of 2014 and patients who received LipoB ICNBs from March 2015 through November 2017. We included patients who underwent thoracic surgery for lung cancer using robotic-assisted thoracic surgery (RATS), video-assisted thoracic surgery (VATS), or traditional open thoracotomy, and documentation of ICNB in the operative note. We collected data on pain scores (Visual Analog Scale [VAS]) and opioid consumption (converted to oral morphine equivalents [OMEs]) intraoperatively, on postoperative day (POD) 0, POD 1, POD 2, and POD 3. We also analyzed data on length of stay [LOS]. A primary analysis was performed on the effects of LipoB vs bupivacaine across all surgery types on opioid consumption, pain scores, and LOS with a secondary analysis on the same endpoints per individual surgery type.

Results: A total of 129 patients were included from the predefined study periods (n = 62 LipoB and n = 67 standard bupivacaine). Across all surgery types, LipoB decreased opioid utilization vs standard bupivacaine ($P < .01$). Post-hoc testing revealed that this difference existed intraoperatively (55 ± 5 vs 69 ± 4 mg OME, $P = .03$) and on POD 0 (44 ± 6 vs 68 ± 6 mg OME, $P < .01$). Surgical subtype analysis revealed that this difference was mostly driven by lower opioid consumption in patients undergoing RATS. When compared across all surgery types, LipoB vs bupivacaine did not affect postoperative pain scores. However, subgroup analysis showed that pain scores were lower in the LipoB vs standard bupivacaine group undergoing VATS on POD 0, 1, and 2. The LOS across all thoracic surgery types was lower in the LipoB group when compared to the standard bupivacaine group (median, 4 days [IQR 2.0-6.0] vs median, 5 days [IQR 3.0-8.0], $P < .01$). Subgroup analysis showed that the LOS in patients undergoing VATS with LipoB ICNBs was shorter compared to patients receiving bupivacaine ICNBs.

Limitations: The retrospective nature of this study makes it prone to several types of bias.

Conclusion: ICNBs with LipoB for thoracic surgery leads to lower opioid consumption and shorter LOS when compared to ICNBs with standard bupivacaine. The benefit of LipoB over standard bupivacaine for ICNBs appears especially relevant in VATS or RATS procedures.

Key words: Intercostal nerve block, liposomal bupivacaine, RATS, regional anesthesia, robotic-assisted thoracoscopic surgery, thoracotomy, VATS, video-assisted thoracoscopic surgery

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Intravenous opioids have been a mainstay of traditional postoperative pain control regimens for patients undergoing thoracic surgery for decades. Regional anesthesia options for postsurgical pain control include intercostal nerve blocks (ICNBs) and thoracic epidural analgesia (TEA). While recent literature has proposed erector spinae plane blocks (ESP) (1) and serratus anterior plane blocks (SAP) (2) for pain control after thoracic surgery, TEA is still considered the gold standard for pain control in the thoracic surgical population (3). Although TEA is effective, pain control can often be inconsistent and is highly dependent on the skill of the operator placing the epidural catheter, as failure rates of over 30% have been reported (4). The use of TEA for pain control after thoracic surgery can also result in higher rates of urinary retention and hypotension, and TEA placement often requires the additional cost of an acute pain service to manage these patients.

Centers without a robust acute pain service have historically used ICNBs with plain bupivacaine to reduce postsurgical pain and intravenous opioid consumption. Pain control via ICNBs, though, has been hampered by the limited duration of block achievable with longer-acting local anesthetics, namely the 18-24 hours of sensory analgesia provided by plain bupivacaine (5).

Liposomal bupivacaine (LipoB) (Exparel, Pacira Pharmaceuticals, Parsippany, NJ) is approved by the US Food and Drug Administration for local wound infiltration, fascial plane infiltration, and interscalene blocks (6,7). LipoB is an emulsion containing multivesicular liposomes consisting of nonconcentric lipid bilayers. Vesicles of bupivacaine loaded in this proprietary DepoFoam® matrix slowly release bupivacaine over 72-96 hours (8). Recent literature (9,10) shows that ICNBs with LipoB may be equivalent to TEA for pain control in patients undergoing thoracic surgery, and lead to a reduction in the length of stay (LOS) for thoracic surgery patients. This positive evidence regarding LOS and pain control, coupled with the ease of use of LipoB, has led to standard bupivacaine being replaced by LipoB for ICNBs in thoracic surgery at our institution. The purpose of this study was to evaluate the impact of this change on postoperative pain control as measured by opioid consumption, postoperative pain intensity, and LOS in patients undergoing thoracic surgery. We hypothesized that the use of LipoB for ICNBs in thoracic surgery leads to improved pain control compared to ICNBs with standard bupivacaine, as evidenced by lower opioid consumption, pain scores, and reduced LOS.

Methods

Study Design

After obtaining approval from the Cooper University Health Care Institutional Review Board (IRB number: 18-001EX), we conducted a retrospective review of ICNBs completed at Cooper University Hospital for thoracic surgery. This report adheres to the STROBE guidelines (11).

Patient Selection

Our institution transitioned to LipoB for ICBNs in the context of thoracic surgery in April of 2014. We therefore enrolled our control group from consecutive patients who underwent thoracic surgery from January 2013 through February of 2014. Patients in the investigational group who received LipoB in their ICNBs had surgery between March 2015 and November 2017. We allowed for a period of one year between inclusion periods to ensure that the transition to LipoB as the standard of care for ICNBs for thoracic surgery had been completed. Patients included in the study were older than 18 years of age and had undergone video-assisted thoracic surgery (VATS), robotic-assisted thoracic surgery (RATS), or open thoracotomy for either segmental wedge or lobe resection for cancer. Patients who had a history of chronic opioid use were excluded. Additionally, patients during this time period in whom we could not clearly ascertain the type of ICNB performed based on the operative note were excluded.

Intercostal Nerve Blocks

Patients included in this study had their operation performed by one of 2 thoracic surgeons at our hospital. Both surgeons use similar surgical approaches and perform ICNBs in a similar fashion. For all cases, ICNBs were performed successively between ribs 4 to 10 on the operative side. In the LipoB group, 266 mg of LipoB was mixed with 20 mL of saline (40 mL total volume) and split between the injection sites from ribs 4 to 10. In the control group, 30 mL of 0.5% plain bupivacaine was split between the ICNB sites. ICNBs were performed under direct visualization immediately after access was gained to the thorax when the VATS or RATS technique was utilized. For thoracotomies, ICNBs at ribs 4 to 10 were performed by palpation prior to surgical incision.

Outcomes

The primary outcome variable studied was opioid consumption (converted to Oral Morphine Equivalent

[OME], mg) in patients who received ICNBs with LipoB, compared to patients who received ICNBs with standard bupivacaine for thoracic surgery via VATS, RATS, or traditional open thoracotomy. OME consumption was compared intraoperatively and on postoperative days (POD) 0, 1, 2, and 3 (if applicable). Secondary outcome measures included postoperative pain (as measured by average Visual Analog Score [VAS] scores on PODs 0-3), and LOS.

Data Collection

All data were collected from electronic health records at Cooper University Hospital. On a data collection sheet, we recorded demographic information, medical history, procedural characteristics, use of opioids intraoperatively and on PODs 0-3, VAS pain scores from PODs 0-3, and time of discharge. Different opioid medication dosages were then converted to OMEs using an opioid analgesic equivalent calculator (12) based on the American Pain Society guidelines (13) and several reviews regarding equianalgesic dosing (14-16). Total OMEs were calculated for the intraoperative period, POD 0, POD 1, POD 2, and POD 3.

Statistical Analysis

Data were analyzed with SPSS Version 24.0 (IBM Corporation, Armonk, NY) and visualized using SigmaPlot Version 12 (Systat Software Inc., Chicago, IL). Categorical data are presented as n (%); continuous variables are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), depending on the distribution of the data. Normality of the data was assessed using the Shapiro-Wilk test. Demographic characteristics, treatment characteristics, and LOS in the bupivacaine and LipoB groups were compared using unpaired t tests, Mann-Whitney U tests, or chi-squared tests. A mixed linear model was used to assess if use of LipoB resulted in differences in OME or pain scores. "Block Type" (bupivacaine/LipoB), "Time" (intraoperative, D0, D1, D2, and D3), and "Access Type" (thoracotomy, VATS, and RATS) were included as fixed factors. "Subject" was included as a random factor. To supplement this analysis, 2-sided post-hoc tests with Bonferroni correction were performed to determine which time point differences existed, if a significant main or interaction effect with $P < .05$ was detected for "Block Type." *P* values are reported for all tests.

Results

A total of 129 patients were included from the predefined study periods. Of these, 67 received intercostal nerve blocks with standard bupivacaine, while LipoB was used for 62 patients (Table 1). Demographic characteristics were comparable between the bupivacaine and LipoB groups, but patients in the LipoB group presented with more comorbidities as evidenced by more prevalent hypertension, congestive heart failure, and diabetes, as well as higher American Society of Anesthesiologists scores. The number of patients undergoing wedge resection or lobectomy was similar in both groups. There was a trend towards patients in the LipoB group undergoing more open thoracotomies and VATS, while undergoing fewer RATS compared to the standard bupivacaine group ($P = .06$). Mean procedure length was similar in both groups: 305 ± 83 minutes in the standard bupivacaine group vs 231 ± 76 minutes in the LipoB group ($P = .32$).

Opioid Utilization

Across all surgery types, LipoB decreased opioid utilization vs standard bupivacaine (Time * Block Type: $P < .01$, Fig. 1). Post-hoc testing revealed that this difference existed intraoperatively (55 ± 5 vs 69 ± 4 mg OME, $P = .03$) and on POD 0 (44 ± 6 vs 68 ± 6 mg OME, $P < .01$). There was a significant interaction between time, block type, and surgery type ($P < .01$), indicating a 2-way interaction that varies across levels of a factor (e.g., the effect of Time * Block Type is different across surgical types), which led us to perform additional analyses in the surgery subtype groups. These analyses demonstrated that opioid utilization was lower in the LipoB group undergoing VATS (POD 2 and POD 3) and RATS (intraoperative and POD 0) (Fig. 2).

Pain

Across all surgery types, block type did not affect postoperative pain scores (Fig. 3). There was, however, a significant interaction between block type and surgery type ($P < .01$) and analyses in the surgery subtype groups showed that pain scores were lower in the LipoB group undergoing VATS at POD 0, POD 1, and POD 2 (Fig. 3).

Length of Stay

The LOS was lower in the LipoB group when compared to standard bupivacaine when all surgical subtypes were analyzed together (median, 4 days [IQR 2.0-6.0] vs median, 5 days [IQR 3.0-8.0]; $P < .01$. When analyzing the individual surgery subgroups, we found that the LOS in patients undergoing VATS with

Table 1. *Characteristics of patients in the liposomal bupivacaine and standard bupivacaine cohorts.*

	Bupivacaine (n = 67)	Liposomal Bupivacaine (n =62)	*P* Value
Patient Characteristics			
Age in yrs, median (IQR)	67 (52-74)	67 (60-74)	.36
Gender, M/F, n (%)	26/41 (39/61)	32/30 (52/48)	.10
Body mass index in kg/m^2, median (IQR)	28 (24-35)	28 (25-32)	.41
American Society of Anesthesiologists status			**.03**
2, n (%)	18 (27)	8 (13)	
3, n (%)	44 (66)	53 (86)	
4, n (%)	5 (8)	1 (2)	
Medical history			
Hypertension, n (%)	38 (57)	52 (84)	<.01
Congestive heart failure, n (%)	7 (10)	31 (50)	<.01
Diabetes mellitus, n (%)	23 (34)	38 (61)	<.01
Procedure Characteristics			
Procedure			.73
Wedge resection, n (%)	25 (37)	25 (40)	
Lobectomy, n (%)	42 (63)	37 (60)	
Access type			.06
Thoracotomy, n (%)	9 (13)	15 (24)	
Thoracoscopy, n (%)	22 (33)	26 (42)	
Robotic, n (%)	36 (54)	21 (34)	
Procedure length in min, mean ± SD	305 ± 83	231 ± 76	.32

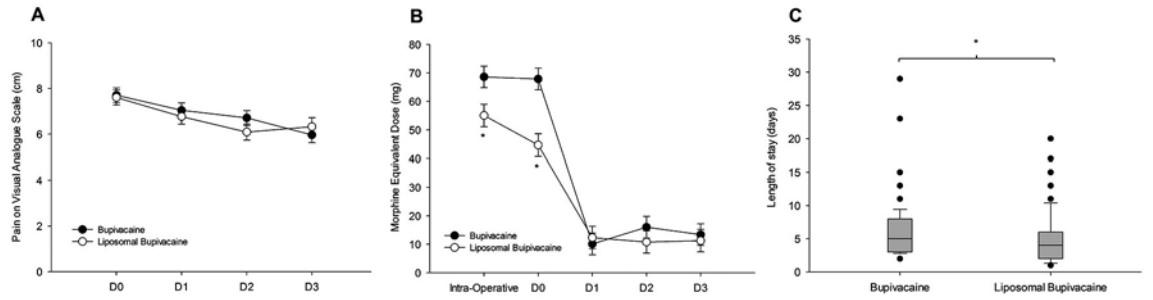

Fig. 1. *Effect of liposomal bupivacaine versus standard bupivacaine across all surgical subgroups.*
Panel A depicts the pain score up to postoperative day 3, panel B depicts the opioid requirements up to postoperative day 3, and panel C depicts the length of stay in liposomal bupivacaine and standard bupivacaine cohorts. Opioid consumption was lower in the liposomal bupivacaine vs standard bupivacaine cohort intraoperatively and on postoperative day 0. Length of stay was shorter in the liposomal bupivacaine vs standard bupivacaine cohort as well. D0 = postoperative day 0; D1 = postoperative day 1; D2 = postoperative day 2; D3 = postoperative day 3; * = $P < .05$.

LipoB ICNBs was shorter than that of patients receiving standard bupivacaine (median, 2.0 days [IQR 1.7-3.0] vs median, 3.5 days [IQR 2.7-7.0]; $P < .01$, Fig. 4).

Discussion

LipoB, a relative newcomer to the regional anesthesia scene, has shown significant promise in control-

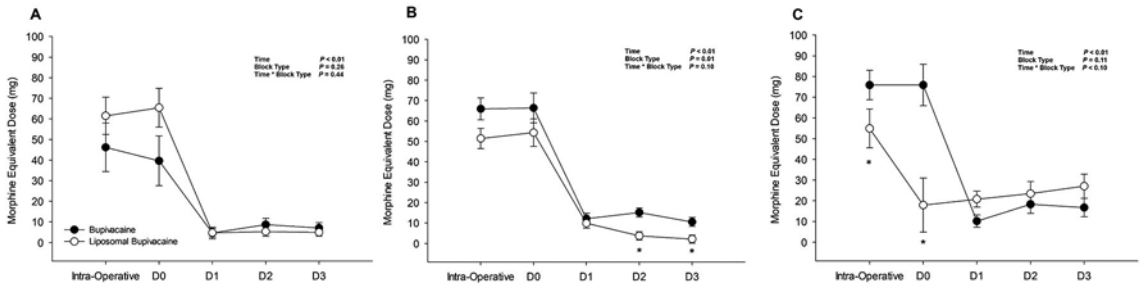

Fig. 2. ***Opioid requirements up to postoperative day 3 for liposomal and standard bupivacaine cohorts in surgical subtype groups.*** Panel A depicts opioid requirements after open thoracotomy procedures, panel B depicts opioid requirements after video-assisted thoracoscopy procedures, and panel C depicts opioid requirements after robotic-assisted thoracic procedures. Opioid requirements were significantly lower in the liposomal bupivacaine vs standard bupivacaine cohort in video-assisted thoracoscopy patients on postoperative days 2 and 3, as well as in RATS patients intraoperatively and on postoperative day 0. D0 = postoperative day 0; D1 = postoperative day 1; D2 = postoperative day 2; D3 = postoperative day 3; * = $P < .05$.

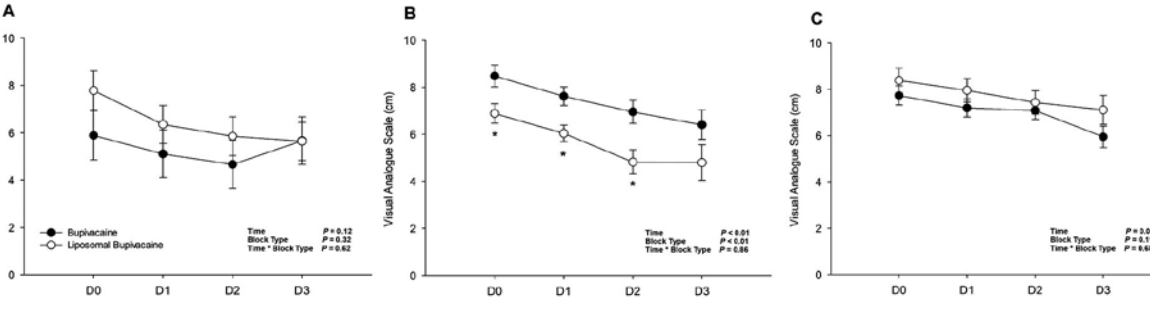

Fig. 3. ***Pain up to postoperative day 3 for liposomal and standard bupivacaine cohorts in surgical subtype groups.*** Panel A depicts pain after thoracotomy procedures, panel B depicts pain after video-assisted thoracoscopy procedures, and panel C depicts pain after robotic-assisted thoracic procedures. Pain was significantly lower in the liposomal bupivacaine vs standard bupivacaine cohort in video-assisted thoracoscopy patients on D0, D1, and D2. D0 = postoperative day 0; D1 = postoperative day 1; D2 = postoperative day 2; D3 = postoperative day 3; * = $P < .05$.

ling pain after several different types of operations, including hemorrhoidectomy, breast surgery, and shoulder surgery (17-20). Although LipoB has been touted for use in thoracic surgery (10), it is still unclear whether this novel formulation of bupivacaine provides an advantage across all subtypes of thoracic surgery. The aim of this study was to evaluate whether LipoB for ICNBs is associated with lower opioid usage, pain scores, and LOS when compared to standard bupivacaine for ICNBs. In our primary analysis looking at all thoracic surgical subtypes combined, results indicate that LipoB is effective in reducing opioid consumption both intraoperatively and on POD 0. Additionally, patients who received LipoB in our study were discharged from the hospital earlier (median for LipoB, 4 days vs median for conventional bupivacaine, 5 days). The overall reduction in opioid consumption we encountered was similar to reductions described by Kelley et al (21) and Parascandola et al (22), who compared the effect of ICNBs with LipoB to ICNBs with standard bupivacaine in patients undergoing VATS. The decrease in LOS we found with LipoB is similar to what Dominguez et al (23) demonstrated in their retrospective study looking at the impact of ICNBs with LipoB vs standard bupivacaine for various VATS procedures. Our secondary analysis of thoracic surgery subgroups (open thoracotomy, VATS, or RATS) demonstrated that the positive overall effects of LipoB vs standard bupivacaine were mostly mediated by differences in VATS and RATS procedures.

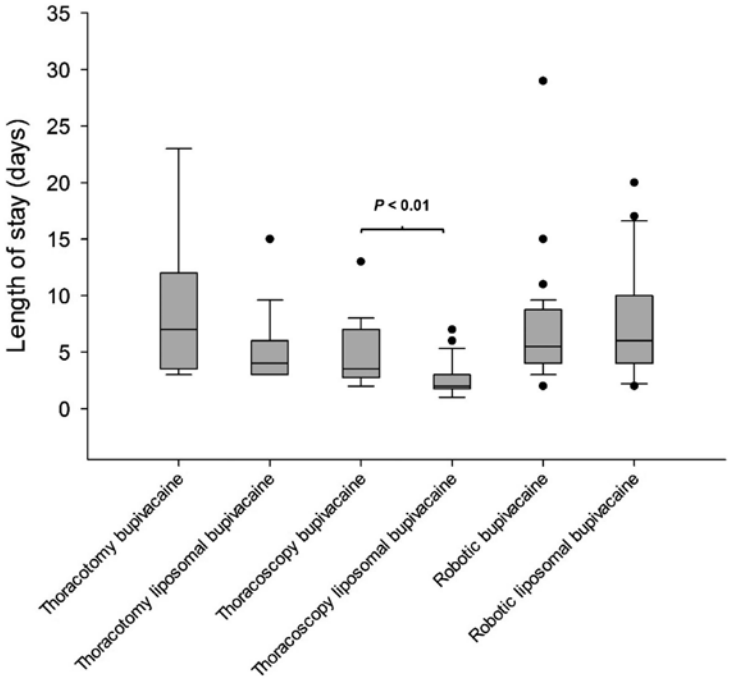

Fig. 4. *Length of stay for liposomal and standard bupivacaine cohorts in surgical subtype groups.*
Length of stay was significantly shorter in the liposomal bupivacaine video-assisted thoracoscopy group vs the standard bupivacaine group. * = $P < .05$.

Thoracotomy

Patients undergoing open thoracotomies benefited the least from ICNBs with LipoB compared to standard bupivacaine in our analysis. There was no difference in pain scores across all measured time points. Opioid consumption did not vary significantly across all time points between the groups, and LOS was not different between the 2 groups either. Patients undergoing open thoracotomies have more pain, and require more opioids than patients undergoing minimally invasive procedures (24-26). Thus, it was unexpected that the patients in the LipoB group, who received the local anesthetic with the longer-lasting profile, did not experience improved pain control for a longer duration. The number of patients studied who underwent open procedures was low in both the standard bupivacaine group (n = 9) and LipoB group (n = 15), and it is possible that there might not have been enough patients studied to reliably assess the effect of LipoB in this surgical subgroup.

VATS

A few studies have evaluated the use of LipoB for ICNBs compared to traditional bupivacaine for VATS procedures (21-23). Kelley et al (21) showed a reduction in opioid use for the first 24 postoperative hours in the LipoB group vs conventional bupivacaine, which was not evident in our study. However, we did encounter a reduction in opioid usage in the LipoB group for VATS procedures on PODs 2 and 3. This is similar to Parascandola et al (22), who showed a reduction in opioid usage from 24 to 72 hours postoperatively in the LipoB group.

A study by Dominguez et al (23) showed higher pain scores with LipoB vs standard bupivacaine over the first 24 hours, whereas our data indicate that the average pain scores in the LipoB group were significantly lower than those in the conventional bupivacaine group for PODs 0, 1, and 2. Dominguez et al postulated that patients who received LipoB had higher pain scores because they were ambulating sooner than those who received standard bupivacaine. Our study did not evaluate time to ambulation. Similar to our findings, Dominguez et al encountered a significantly lower LOS in the group that received LipoB.

RATS

In patients undergoing RATS, our analyses of 57 patients showed a reduction in opioid consumption for patients in the LipoB group intraoperatively and on POD 0. The data did not indicate any meaningful differences in pain scores between groups across all time points. Only one previously published study has directly compared the use of LipoB ICNBs to ICNBs with plain bupivacaine in robotic thoracic surgery (27). Rincavage et al did not encounter any difference in pain scores, opioid usage, or LOS in their retrospective analysis of 96 patients, but they did show a reduction in nonsteroidal anti-inflammatory medication usage on POD 1.

Our retrospective analysis revealed some findings that were consistent with our hypothesis, while there were some unexpected findings as well. When taken as a whole, our analysis showed a consistent benefit of LipoB ICNBs when compared to ICNBs with plain bupivacaine. We encountered a reduction in opioid consumption intraoperatively and

on POD 0 as well as a reduction in the LOS in patients receiving ICNBs with LipoB. The reduction in opioid consumption and LOS took place without seeing any differences in pain scores between the groups across all surgical types. Unexpectedly, in the subgroup analysis, opioid requirement and pain score trends were not consistent across all surgical subtypes. Reductions in LOS were not uniform across all subtypes of thoracic surgery either. The predominant beneficial effect of LipoB ICNBs vs conventional bupivacaine ICNBs appeared to be in VATS and RATS. This finding is consistent with prior reports in this area (21-23).

Limitations & Methodological Considerations

As a retrospective review, this study carries the limitations of potential selection bias and time bias. A medical practice is generally evolving over time; while we looked for any glaring changes in practice over the 4-year time frame of this study, we may have missed smaller contributory changes in practice that may have led to the positive impact we attributed to the LipoB. Additionally, while we limited our review to the practice of just 2 surgeons, we cannot rule out the continual improvement in their surgical technique as part of the reason for our positive outcomes.

Our retrospective analysis had sicker patients in the LipoB group, as there was a significant difference noted in the number of patients who carried diagnoses of hypertension, heart failure, or diabetes when compared to the bupivacaine group. This was unexpected, as we included consecutive patients who met the inclusion criteria for each group. The increase in the number of patients with comorbid diseases is not readily explainable, but it is important to note that we did find a shorter LOS in the LipoB group despite this difference.

We found lower opioid utilization intraoperatively and on POD 0 for LipoB vs standard bupivacaine. This appears to run counter to the sustained-release purpose and the structural properties of LipoB, which may be expected to hamper sufficient early release. Gadsden and Long (28) reviewed the literature regarding time-to-onset of analgesia observed with LipoB vs standard bupivacaine as well as pharmacokinetic studies comparing the 2. They found similar time-to-onset with LipoB and standard bupivacaine, with LipoB typically demonstrating superior analgesic efficiency even at the earliest time points after surgery. Plasma pharmacokinetic parameters of LipoB vary significantly dependent on the anatomical location of injection and are not correlated with local efficacy (29). Our findings of early benefits of LipoB vs standard bupivacaine are consistent with the study of VATS surgery by Dominguez et al (23). Admixture of standard bupivacaine with LipoB has been reported (30) and is aimed to address a hypothesized early analgesic gap. Clinical studies on admixing will likely clarify if there is any additional value in using the combination of LipoB and standard bupivacaine vs LipoB alone.

Conclusion

This retrospective analysis comparing pain control via ICNBs in thoracic surgery showed that use of LipoB reduced opioid consumption and LOS for patients when compared to plain bupivacaine. The effects of LipoB vs conventional bupivacaine were most pronounced in VATS, when the data were analyzed for each subtype of surgery. Our findings are consistent with previous studies on ICNBs with LipoB for VATS and RATS and support its use for these procedures. A prospective randomized controlled trial evaluating the effectiveness of ICNBs with LipoB is warranted to confirm its superiority in pain control after thoracic surgery when compared to ICNBs with standard bupivacaine.

Author Contributions

KMP and NvH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KMP, KT, and RGD designed the study protocol. KMP managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. NVH, GMK, AP, FWB, DS, KT, and RGD provided revision for intellectual content and final approval of the manuscript.

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