

Efficacy Of Liposomal Bupivacaine For Pain Control In Pediatric Patients With Adolescent Idiopathic Scoliosis Undergoing Instrumented Posterior Spinal Fusion

Vishal Sarwahi MD¹, Alexander Morledge BA¹, Anabelle Cohen BS¹, Katherine Eigo BA¹, Effat Rahman BS¹, Sarah Trent MD¹, Swara Kalva BS², Viraaj Sarwahi¹, Jon-Paul DiMauro MD¹, Jeremy Nikfarjam MD¹, Yungtai Lo PhD³, Terry Amaral MD¹

¹ Northwell Health, Cohen Children's Medical Center Department of Pediatric Orthopaedics, New Hyde Park, NY

² Donald and Barbara Zucker School of Medicine, Hempstead, NY

³ Albert Einstein College of Medicine, Bronx, NY

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Corresponding Author:

Vishal Sarwahi, MD
Department of Pediatric Orthopaedics
7 Vermont Drive
New Hyde Park, NY 11042
P: 516-210-8402
E: vsarwahi@northwell.edu

Structured Abstract

Study Design Retrospective Cohort Study

Objective This study aimed to compare perioperative pain outcomes in Adolescent Idiopathic Scoliosis (AIS) patients who either did or did not receive a liposomal bupivacaine (LB) injection during their posterior spinal fusion (PSF).

Summary of Background Data Liposomal bupivacaine (LB) has been promoted for its apparent long-lasting effects on pain management when compared to standard formulations. Many studies in adult spine populations have been carried out with varying results but few studies have investigated LB's effect in the pediatric population.

Methods: 472 pediatric patients with spine deformity undergoing posterior spinal fusion (PSF) between 2018 – 2024 were included. Starting early 2018, patients began receiving peri-incisional injections of LB by plastic surgeons during PSF closure (LB Group). These patients were compared to those that did not receive any injections (Non-LB [N-LB] Group). Pain scores, opioid consumption (MME), time to ambulation (out-of-bed/OOB), length of stay (LOS), narcotic refills, and 90- day complications were analyzed. Differences between the LB and N-LB groups were assessed using the Wilcoxon rank-sum test for continuous variables and either the chi-square test or Fisher's exact test for categorical variables, as appropriate. A non-parametric analysis of covariance (ANCOVA) was conducted to compare pain scores at rest on POD1 and POD2, as well as morphine consumption during the first 24 hours and total morphine consumption.

Results: 295 patients were in the LB Group, and 177 patients were N-LB. No differences were noted in demographics. Pain scores at rest were significantly lower on POD 1, POD 2, and overall ($p < 0.05$) in LB patients. LOS was significantly shorter in LB patients ($p < 0.001$).

Significantly more patients were out of bed by POD 0 (59.9% vs 38.0%, $p < 0.001$) in the LB group. LB patients consumed significantly less opioids in 0-24 hours postop and during their total hospital stay ($p < 0.001$ and $p = 0.032$, respectively).

Conclusion: Patients who received liposomal bupivacaine had lower VAS pain scores at rest, opioid consumption, and length of stay with no increase in complications. This suggests that a long-acting local anesthetic formulation may offer superior pain management.

Key Points

1. Liposomal bupivacaine (LB) group consumed 39.5 MME compared to the N-LB group consuming 56.5 MME in the 0-24H timeframe ($p < 0.001$)
2. Liposomal bupivacaine (LB) group consumed 140.2 MME compared to the N-LB group consuming 161.4 MME for total morphine consumption overall ($p = 0.032$)
3. Liposomal bupivacaine (LB) group had significantly lower overall Max Pain Score at Rest (6) than N-LB group (8) ($p < 0.001$).

Introduction

Opioids are commonly prescribed for pain management after scoliosis surgery in pediatric patients and are often given intravenously as patient controlled analgesia (PCA). However, opioids carry the risk of respiratory depression, increased likelihood of future misuse, constipation, and drowsiness. The use of microdose intrathecal morphine has been shown to reduce opioid exposure in this population. The American Society of Anesthesiologists (ASA) recommends a multimodal pain regimen including local anesthetics, such as ropivacaine hydrochloride and bupivacaine hydrochloride are approved in the adult population.

Liposomal bupivacaine (LB) is a long-acting anesthetic composed of a phospholipid bilayer encapsulating the bupivacaine to allow its slow release of the drug, lasting up to 72 hours.⁵⁻⁷ LB has two peak concentrations, one immediately after injection, and another 10-36 hours later.⁸ Liposomal bupivacaine's use in spine surgery has shown promising results and is now FDA-approved for use in pediatrics.

Changoor et al compared 53 AIS patients undergoing posterior spinal fusion (PSF) who received LB to 66 who did not.⁶ LB patients consumed less opioids, ambulated farther, and had shorter stay.⁶ This study aims to investigate LB in a larger group of adolescent spinal deformity patients undergoing PSF. Our institution utilizes microdose intrathecal morphine and has eliminated the use of PCA, which has decreased opioids by over 70%.⁹ We hypothesized that LB provided longer lasting pain control, improved perioperative outcomes, and further decreases opioid consumption compared to those who did not receive intraoperative LB.

Materials and Methods

This was an Institutional Review Board-approved retrospective chart review of 472 pediatric patients with spine deformity undergoing PSF at a single institution from 2018-2024. All patients were < 18 years old and had complete medical records. Neuromuscular, syndromic, and non-idiopathic scoliosis patients were excluded. Descriptive statistical analysis was used to compare a patient group which received liposomal bupivacaine (LB) against those who did not receive liposomal bupivacaine (N-LB). Bupivacaine is an amide local anesthetic which acts by inactivating voltage-gated sodium channels. Compared to lidocaine, its slower release from its binding site prolongs its duration of action.¹⁷ Liposomal bupivacaine's multilayer structure of drug encapsulation increases stability and longer duration of drug release compared to conventionally formulated bupivacaine.⁵ Thus, the pharmacokinetic profile exhibits a biphasic, dose-related release model. The initial peak is within 1 hour of administration and is related to extra-liposomal bupivacaine in the formulation. Subsequent peaks occur at 12 and 48 hours later and correspond to the release of LB.¹⁷⁻¹⁹

Data Collection and Measurements

Demographic characteristics, including age, sex, and BMI, were collected. Radiographic measurements include preoperative and postoperative Cobb angles as well as the number of levels fused.

Intraoperative surgical variables included estimated blood loss (EBL), rate of transfusions, opioid consumption, and operative time. Other clinical variables include rate of narcotic refill, number of postoperative days to out-of-bed (OOB), and total length of stay (LOS) via standardized nursing documentation. Opioid consumption was collected as intraoperative opioids, 0-24 hour postoperative opioid consumption, and overall consumption, then converted

to morphine milligram equivalents (MME). Daily maximum Visual Analog Scale (VAS) pain scores were collected at rest and during activity. In accordance with the standardized Rapid Recovery Protocol, their pain was evaluated regularly at two time points each morning.⁹ The nursing staff uses the same pain scoring system when patients were receiving more medications or during bouts of exceptional pain. Utilizing patient reported scores, an average maximum pain score was calculated both at rest and at activity.

90-day complication rates were analyzed and some complications included symptoms such as dizziness, fever, urinary retention, or wound drainage issues. Total cost was comprised of intraoperative anesthesia, postoperative anesthesia, operating room time, ICU stay, and hospital stay costs.

Perioperative Pain Protocol

Both groups followed the standardized rapid recovery pathway (RRP) protocol, implemented at this institution in 2018. This protocol includes direct guidelines for medication administration, physical therapy, and mobility checkpoints. The patient and family are educated on postoperative recovery, realistic pain expectations, and the drawbacks of opioid use.⁹ Patients should increase physical activity and maintain a high-fiber diet leading to surgery. Patients receive a clear carbohydrate drink (Ensure presurgery) 2-hours before surgery. The recommendations are reinforced at surgical discussion, pre-surgical testing, anesthesia work up, and at child life and social work evaluation. Recovery and Ambulation protocols remained unchanged throughout the entire retrospective study.

The patient starts on PO oxycodone and diazepam on POD0. IV ketorolac started 6 hours after OR dose (0.5 mg/kg). Patients are given either acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) every 2 hours. Acetaminophen is given at hour 8, 12, 16, while an NSAID is staggered at hour 10, 14 and 18.⁹

On POD0, patients start bed mobility training and sitting up in bed if tolerated alongside physical and occupational therapy. On POD1, the patient is OOB to chair and beginning to ambulate as tolerated. On POD2, the patient ambulates in room and hallway 2-3x/day.⁹ On POD3, the patient utilizes the stairs with a physical therapist, and pain is managed with acetaminophen and diazepam, oxycodone is changed to PRN. Patients are typically discharged by POD3 with diazepam, PO oxycodone PRN, and acetaminophen. A standard dose of 3-5 days of opioids are prescribed to the patient.⁹

Intraoperative Technique

Intrathecal morphine (ITM) is administered as 1.5 µg/kg diluted in 1 to 1.5cc of saline by anesthesiologists at the beginning of the case or by the orthopedic surgeon at the end of the procedure through the interlaminar space (L3–L4 or L4–L5). At induction, IV fentanyl (0.5–2 µg/kg) is given, followed by remifentanyl (0.05–0.5 µg/kg/min) or fentanyl (0.5-2.0 µg/kg/h) infusion.⁹ Immediate postoperative IV ketorolac (0.5 mg/kg; max 30 mg), oral Tylenol (15 mg/kg; max 650 mg), and oral Diazepam (0.05 mg/kg) Q6H are administered for the initial 48 hours. PO oxycodone (0.1 mg/kg) is given Q4H for 72 hours post-surgery. IV hydromorphone (15mcg/kg) Q4H is given for breakthrough pain in the first 24 hours. Starting in early 2018, some patients began receiving injections of LB during wound closure. Those in the LB group received a 20-cc dose of liposomal bupivacaine and 20-cc of 0.25% bupivacaine, one-third of

this dose is injected into the fascia and two-thirds is sub-cutaneous. This technique, known as infiltration, was in accordance with field blocking and volume expansion for LB administration. For patients weighing less than 60 kg, this dose is halved. Those in the N-LB group received 0.25% bupivacaine. Both intubation and extubation protocols were strictly followed.

Statistical Analysis

Data were presented as medians with interquartile ranges, means with confidence intervals for continuous variables, and frequencies with percentages for categorical variables. Differences between the LB and N-LB groups were assessed using the Wilcoxon rank-sum test for continuous variables and either the chi-square test or Fisher's exact test for categorical variables, as appropriate.

A non-parametric analysis of covariance (ANCOVA) was conducted to compare pain scores at rest on POD1 and POD2, as well as morphine consumption during the first 24 hours and total morphine consumption. This rank-based ANCOVA method analyzes ranked rather than raw data, allowing for adjustment of potential confounders. Confounders adjusted included the number of levels fused, preoperative Cobb angle, duration of surgery, duration of anesthesia, pain score on postoperative day (POD0), and intraoperative morphine consumption. These variables were selected based on initial comparisons between the LB and N-LB groups, as well as their clinical relevance.

All statistical analyses were performed by an independent biostatistician using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Two-tailed p-values < 0.05 were considered statistically significant.

Results

295 patients received liposomal bupivacaine (LB group) during their spinal fusion and 177 patients did not (N-LB). Median age for LB patients was 15.3 years, BMI was 21.5, and 67.1% were female. Median age in N-LB was 15.2 years ($p=0.67$), BMI was 21.0 ($p=0.31$), and 69.6% were female ($p=0.57$). Median Cobb angle was 52.2° in LB, postoperative Cobb was 15.2° , and Cobb correction was 72.1%. Median Cobb angle in N-LB was 55.0° ($p=0.002$), postoperative was 18.0° ($p=0.008$), and Cobb correction was 67.9% ($p=0.03$). Levels fused were significantly higher ($p<0.001$) in N-LB than LB groups (Table 1).

Perioperative Variables

Surgery and anesthesia times were significantly higher in N-LB patients compared to LB, (248.0 vs. 240.0, $p=0.04$ and 373.0 vs 388.0, $p=0.005$). There were no significant differences between estimated blood loss between the two groups. The VAS pain scores at rest on POD1, POD2, and overall were lower in LB than in N-LB ($p=0.005$, $p<0.001$, $p<0.001$ respectively). Overall pain scores at activity were not statistically significant between the two groups. LB patients were OOB earlier ($p<0.001$). LOS was significantly shorter among LB patients at median (Q1, Q3) of 4 days (3,5) compared to 4 days (4,5) ($p<0.001$) (Table 2). (Figure 1 and Figure 2).

On non-parametric analysis of covariance (ANCOVA) adjusted for levels fused, preop Cobb angle, surgery time, anesthesia time, pain scores at activity POD0, and intraoperative morphine consumption, patients in the LB group had significantly lower 0-24h morphine consumption ($p = 0.001$) but no significant difference in total morphine consumption (Table 4). Furthermore, LB group had no significant difference in VAS pain scores at rest on POD1

($p=0.628$) but had significant differences on POD2 ($p<0.001$) as well as overall pain scores ($p<0.001$) compared to the N-LB group (Table 5).

Opioid Consumption

There was no significant difference between the LB and N-LB group for intraoperative morphine consumption. LB patients consumed significantly less opioids during the first 24 hours after surgery ($p<0.001$). LB patients consumed a total of 140.2 MME, significantly less than 161.4 MME consumed by N-LB patients ($p=0.03$) (Table 3) (Figure 3).

Cost Analysis

A subgroup of all LB and N-LB patients was selected from 2019-2020. A cost-analysis was conducted analyzing the differences between intraoperative anesthesia, post-operative anesthesia, ICU Stay, Entire Hospital Stay (sum of ICU and PACU days), Operating Room, and the total overall in United States Dollars (USD). There were no significant decreases in Intra-op or Post-op Anesthesia or ICU Stay Cost ($p=0.305, p=0.551, p=0.556$). The N-LB group had a significantly lower operating room cost than the LB group (medians of \$12,437 vs. \$14,274, $p=0.009$). Total hospital stay in the LB group showed a median \$7,190 reduction in cost (\$48,190 vs \$55,380, $p=0.180$), yet this was not statistically significant. The median values showed almost a \$3,000 overall reduction in total cost between groups, although not significantly (\$66,710 vs. \$69,678, $p=0.411$). The groups within the 2019-2020 period are contemporaneous since about 21% of 82 total patients in 2019 were in the LB group and about 23% of 56 patients in 2020 were in the N-LB group.

Discussion

Effective postoperative pain control is an important quality measure in pediatric spine surgery which reduces morbidity and improves functional recovery.¹⁰ Our institution's standardized RRP protocol for pediatric PSF employs multimodal analgesia, however opioid medications continue to play a prominent role in pain relief. Adolescents who are exposed to opioids have an increased risk of 33% for developing opioid dependency.¹¹ The unfavorable side effect profile of opioids including nausea, vomiting, respiratory depression, and ileus also calls into question whether safer and more tolerable forms of analgesia can be incorporated into postoperative care.

In this study, we introduced LB to our multimodal pain control regimen following PSF for AIS. LB group had a significantly lower 'at rest' pain score on POD1, POD2, and overall hospital stay, but not overall pain scores at activity. Postoperative pain was better controlled in the LB group through opioid consumption, showing a 30% difference in average MME within 0-24 hours, and 14% reduction in overall morphine consumption. The pharmacokinetic profile of LB provides additional evidence to support that our results are indeed a reflection of the pharmacodynamic effects of the drug as well as its advantageous analgesia compared to the control.

Chughtai et al. in 2020 evaluated the effects of LB in 323 pediatric patients undergoing spinal deformity correction. They found that LB was associated with significantly lower pain scores throughout POD0 to POD3, though not on POD4.²⁰ The LB group also exhibited less overall and daily opioid consumption when stratified from POD0 to POD3.²⁰

Changoor et al. evaluated LB as an erector spinae block in 119 AIS patients undergoing PSF.⁶ LB group received less opioids overall, required less IV morphine on POD0 and less oxycodone on POD1 and POD2.⁶ LB group contained a higher proportion of patients who used

only oral opioids (81% vs. 41%), while majority of patients who required IV pain control (79%) did not receive LB.⁶ No differences in pain scores were reported despite the minimization of opioid consumption.⁶ In comparison, our surgical technique used LB as field blocks, supplying LB to the patient's entire posterior wound. Additionally, LB's volume was expanded with saline solution to extend coverage to the larger surgical area. Our method involves peri-incisional administration of LB, which is simpler in technique and less time consuming but appears as effective. With this technique, we found a significant decrease in pain scores at rest, as well as opioid consumption at 0-24 hours postoperatively and total opioid consumption.

In 2018, our institution implemented a standardized RRP protocol for AIS patients undergoing PSF that includes both LB and ITM.⁹ Pulido et al. recently compared the combination of LB and ITM versus ITM alone in pediatric patients undergoing PSF for AIS.²¹ Both inpatient and postoperative opioid prescription were decreased significantly than the control.²¹

Although it appears that LB plays a role in limiting opioid use, our findings suggest no overall difference in activity pain compared to the N-LB group. The slow release of LB and delayed peak effect may not suffice for situations in which immediate and potent pain control is needed. We also found that patients in the LB group had significantly earlier OOB times and shorter LOS.^{6,13,22} It is reasonable to hypothesize that patients receiving LB experience less pain and thus ready to mobilize earlier and subsequently be deemed ready for hospital discharge sooner. The existing literature exploring LB use in pediatric spine surgery has generally shown shorter LOS.^{6,20-22}

Time to mobilization and discharge has the potential for health care cost savings. Cost analyses in adult spine have found that LB may decrease total cost of care despite concerns regarding cost of LB (approximately \$280 per vial) compared to standard bupivacaine (approximately \$2 to \$8 per vial).²³ One study showed that LB usage in adult lumbar spine fusion patients was associated with \$218 higher pharmacological cost but an overall \$3035 lower cost for the entire hospitalization, which was significantly shorter in the LB group ($p < 0.001$).²⁴ The earlier discharge results and mobilization results of the present study are promising and could coincide with cost savings for the institution, offsetting the increase in pricing due to LB.

In our study, total hospital stay cost in the LB group suggested a lower median price due to shorter LOS. Further cost-analysis is needed to determine whether the addition of LB in surgery shows a significant cost reduction overall. This overlap between contemporaneous groups shows that both groups were treated using uniform protocol with comparable administration rates, minimizing the likelihood that significant differences in LOS and OOB times between the two groups are due to increasing familiarity with the RRP protocol.

The nature of some patients' 90-day complications could be correlated to the use of LB, particularly symptoms such as: dizziness, fever, urinary retention, or localized, delayed wound healing. However, less than 10% of our LB receiving patient population experienced a 90-day complication.

Evaluating the efficacy of LB in postoperative pain control for pediatric spine deformity surgery is still limited. Our study contributes to the growing support of LB utilization in PSF for AIS. The present study shows LB to be an effective adjunct analgesic to our RRP protocol; it is associated with decreased reported pain levels, reduced consumption of opioid medications in the hospital, quicker time to OOB, and overall shorter LOS. Additionally, cost remains an

important concern, although lower but not significant, aligning with the RRP approach. Most importantly, liposomal bupivacaine administration in addition to the RRP protocol helps decrease opioid consumption in this teenage patient population, thus preventing long term opioid misuse while maintaining comparable/lower pain scores in the immediate post-operative period. Future investigations should aim to assess long-term functional outcomes, perform larger scale cost-effectiveness analyses, and compare LB with other local anesthetic techniques.

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Figure 1. Box and Whisker Plot for Pain Scores at Activity by LB and N-LB

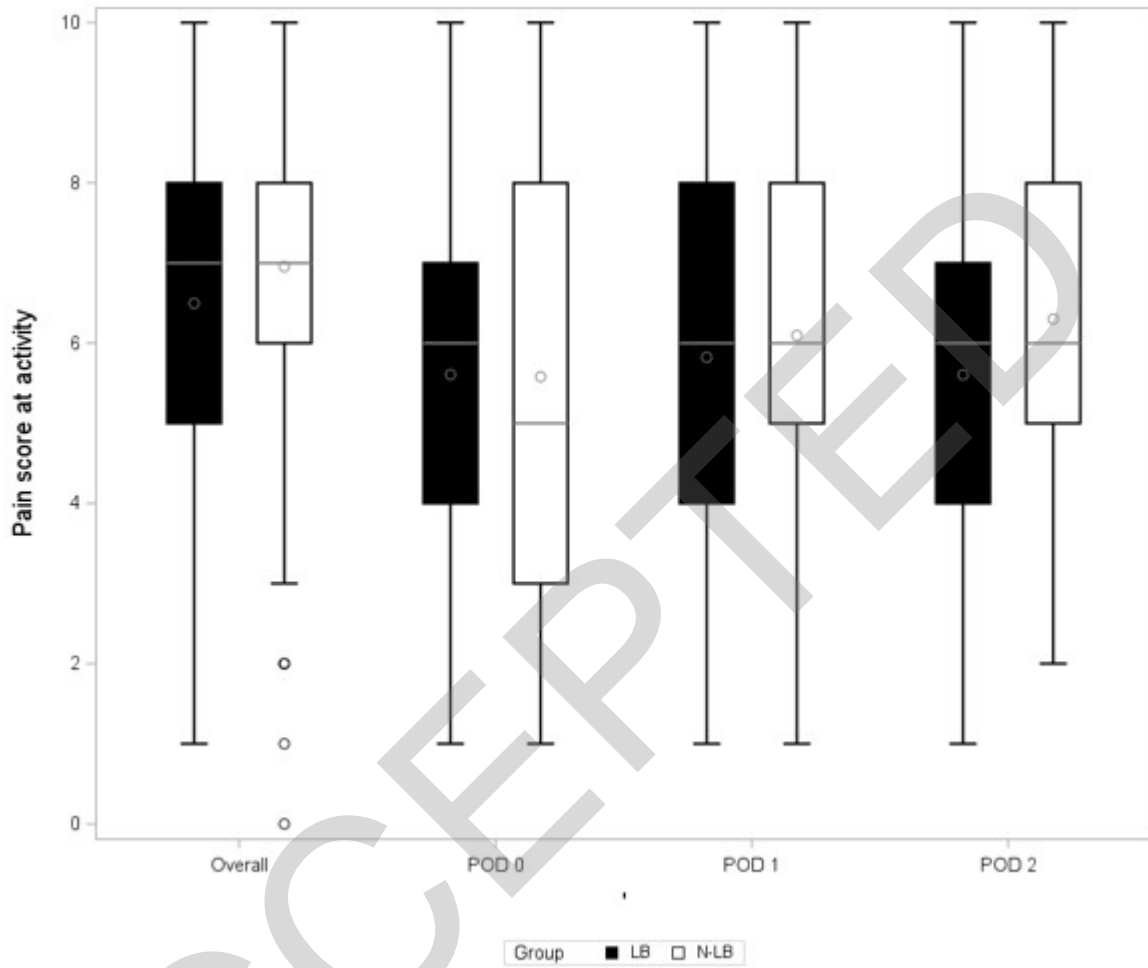


Figure 2. Box and Whisker Plot for Pain Scores at Rest by LB and N-LB

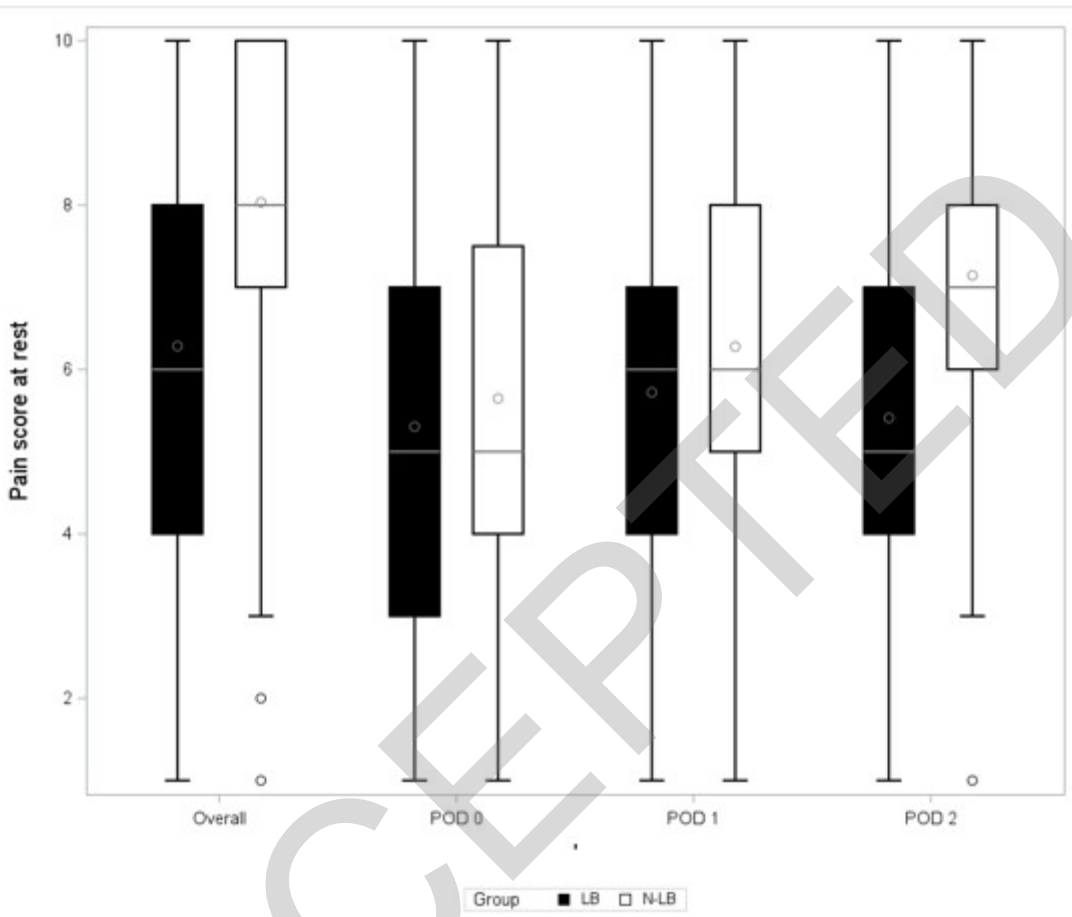


Figure 3. Box and Whisker Plot for Morphine Consumption (MME) by LB and N-LB

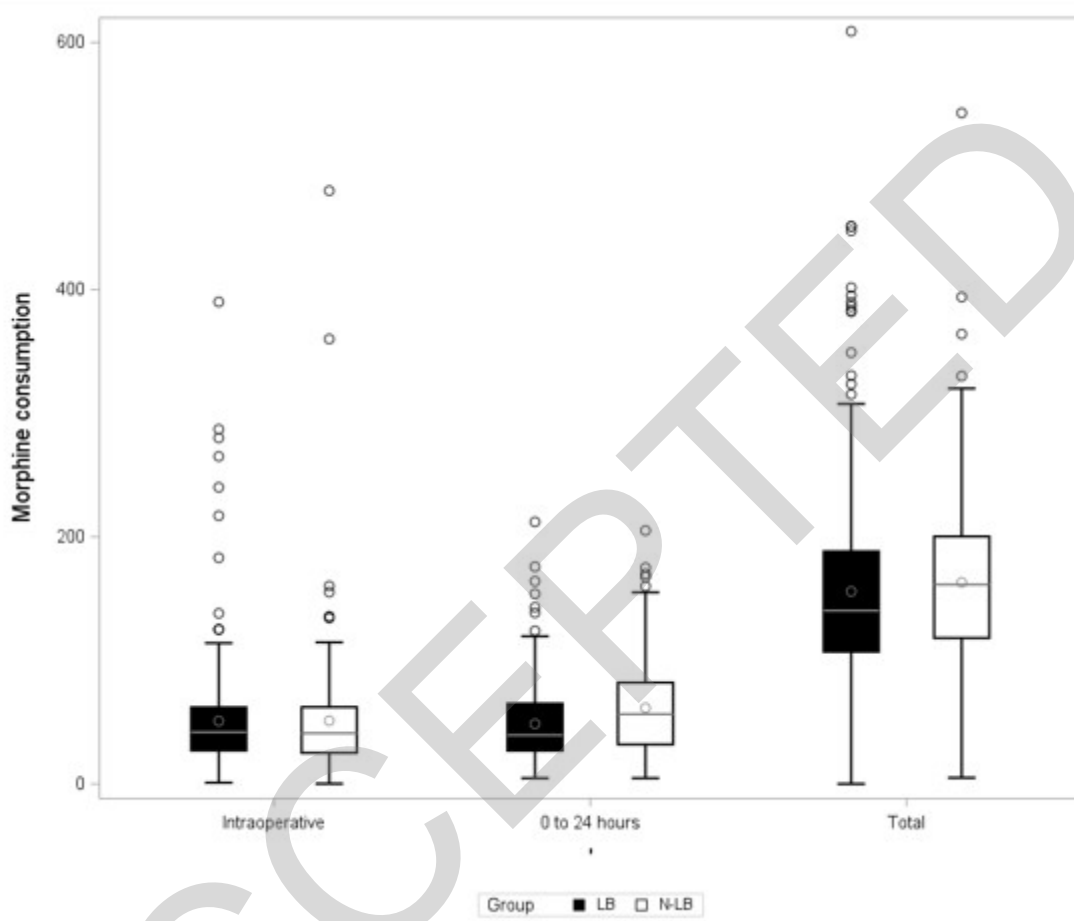


Table 1. Comparison of demographic, radiographic, hospital course, and surgical outcomes variables between AIS patients who received liposomal bupivacaine and those who did not. Data is presented as medians with interquartile ranges and means with standard deviations. P-values < 0.05 are considered statistically significant and bolded.

	LB (n = 295)	N-LB (n = 177)	P
Age (years)	15.3 (14.0, 17.0) 15.6 ± 2.9	15.2 (13.8, 17.0) 15.5 ± 2.7	0.666
BMI (kg ² /m)	21.5 (19.5, 24.9) 22.7 ± 5.5	21.0 (18.9, 24.4) 22.3 ± 5.3	0.311
Female, n(%)	198 (67.1%)	126 (69.6%)	0.571
Preop Cobb (°)	52.2 (45.9, 60.9) 53.9 ± 14.1	55.0 (51.0, 61.0) 56.7 ± 10.9	0.002
Postop Cobb (°)	15.2 (9.2, 21.4) 16.1 ± 9.0	18.0 (13.0, 22.0) 17.8 ± 7.8	0.008
Cobb Correction (%)	72.1 (61.0, 79.8) 70.4 ± 15.9	67.9 (61.3, 75.5) 68.7 ± 12.3	0.025
Levels Fused	12 (11, 13) 12.1 ± 1.8	13 (11, 14) 12.8 ± 2.2	< 0.001
EBL (mL)	400 (300, 625) 530.1 ± 640.0	400 (300, 600) 474.1 ± 294.5	0.252
Surgery Time (mins)	240 (208, 289) 251.9 ± 60.6	248 (221, 312) 267.1 ± 74.8	0.043
Anesthesia Time (mins)	373 (330, 426) 389.5 ± 124.9	388 (350, 453) 404.1 ± 75.4	0.005
Total Transfusions, n(%)	64 (21.7%)	32 (17.8%)	0.302
OOB			< 0.001
POD 0	169 (59.9%)	68 (38.0%)	
POD 1	90 (31.9%)	71 (39.7%)	
POD 2	18 (6.4%)	31 (17.3%)	
POD 3	4 (1.4%)	7 (3.9%)	
POD 4	1 (0.4)	2 (1.1%)	
LOS (days)	4 (3, 5) 4.2 ± 2.7	4 (4, 5) 4.4 ± 1.4	< 0.001
Narcotic refill, n(%)	63 (22.3%)	22 (17.7%)	0.302
90 day return to ED, n(%)	16 (5.4%)	8 (4.5%)	0.300

P values were obtained from Wilcoxon rank-sum tests to compare the medians of continuous variables and chi-square test for categorical variables.

Table 2. Comparison of VAS Pain Scores as well as of milligram morphine equivalence (MME) between AIS patients who received liposomal bupivacaine and those who did not. Data is presented as medians with interquartile ranges, means with standard deviations, and 95% confidence intervals. P-values < 0.05 are considered statistically significant and bolded.

	LB (n = 295)	N-LB (n = 177)	95% C.I. for the difference in medians	P
Max Pain Score At Activity				
<i>POD 0</i>				
<i>POD 1</i>	6 (4, 7), 5.6 ± 2.4	5 (3, 8), 5.6 ± 2.8	0 (-1, 1)	0.789
<i>POD 2</i>	6 (4, 8), 5.8 ± 2.4	6 (5, 8), 6.1 ± 2.3	0 (0, 1)	0.430
<i>Overall</i>	6 (4, 7), 5.6 ± 2.3	6 (5, 8), 6.3 ± 2.1	1 (0, 1)	0.085
	7 (5, 8), 6.5 ± 2.4	7 (6, 8), 7.0 ± 2.3	0 (0, 1)	0.116
Max Pain Score At Rest				
<i>POD 0</i>				
<i>POD 1</i>	5 (3, 7), 5.3 ± 2.4	5 (4, 7.5), 5.7 ± 2.5	0 (0,1)	0.371
<i>POD 2</i>	6 (4, 7), 5.7 ± 2.3		1 (0, 1)	0.05
<i>Overall</i>	5 (4, 7), 5.4 ± 2.4	6 (5, 8), 6.3 ± 2.1	2 (1, 2)	< 0.001
	6 (4, 8), 6.3 ± 2.5	7 (6, 8), 7.1 ± 1.8	2 (1, 2)	< 0.001
		8 (7, 10), 8.0 ± 1.9		
Intraoperative Morphine (MME)	41.9 (27.1, 62.0) 50.9 ± 43.6	41.0 (25.2, 62.2) 51.2 ± 49.7	0.1 (-4.9, 4.2)	0.837
0 – 24H Morphine (MME)	39.5 (26.9, 65.0) 48.6 ± 30.5	56.5 (32.0, 82.0) 61.5 ± 38.4	11.2 (5.0, 17.5)	< 0.001
Total Morphine Consumption (MME)	140.2 (106.9, 188.2) 155.8 ± 81.0	161.4 (118.0, 200.2) 163.1 ± 72.2	13.8 (1.2, 26.2)	0.032

P values were obtained from Wilcoxon rank-sum tests for comparing medians between two groups.

The 95% confidence interval for the difference in medians was obtained using the Hodges–Lehmann method.

Table 3. Cost analysis Liposomal Bupivacaine versus Standard (LB v N-LB) between contemporaneous years of **2019 and 2020**. Data is presented as medians with interquartile ranges and means with standard deviations. P-values < 0.05 are considered statistically significant and bolded.

	LB (N=60)	N-LB (N=78)	p-value
Intra-op anesthesia total cost (\$)	2803 (2494, 3111) 2844 ± 513	2842 (2598, 3225) 2925 ± 541	0.305
Postop anesthesia total cost (\$)	232 (190, 287) 249 ± 95	239 (185, 320) 271 ± 134	0.551
ICU Stay Cost (\$)	30780 (15390, 46170) 30011 ± 18886	30780 (15390, 46170) 30780 ± 16074	0.556
Entire Hospital Stay cost (\$)	48190 (39990, 62065) 51877 ± 14145	55380 (39990, 69760) 55590 ± 16544	0.180
Operating Room Cost (\$)	14274 (12222, 16182) 14546 ± 3432	12437 (10868, 15166) 13091 ± 2374	0.009
Total Cost (\$)	66710 (57824, 79744) 69517 ± 14922	69678 (60585, 84636) 71877 ± 16850	0.411

P values were obtained from Wilcoxon rank-sum tests for comparing medians between two groups.

Table 4. Estimated effect sizes on the rank scale from the non-parametric ANCOVA of Liposomal Bupivacaine (LB) on morphine consumption at 0–24 hours and total morphine consumption adjusted for levels fused, preoperative Cobb angle, surgery duration, anesthesia duration, pain score at activity on POD0, and intraoperative morphine consumption. The coefficients represent adjusted differences in mean ranks between the LB and N-LB groups, or per unit increase in the covariates.

	0-24h morphine consumption		Total morphine consumption	
	Effect size (95% C.I.)	P value	Effect size (95% C.I.)	P value
Liposomal Bupivacaine (LB)	-88.3 (-139.8, -36,8)	0.001	-31.7 (-77.6, 14.2)	0.173
Intraoperative morphine consumption	-0.1 (-0.8, 0.6)	0.827	1.5 (0.9, 2.2)	< 0.001
Levels fused	-7.8 (-21.0, 5.5)	0.247	-7.5 (-19.6, 4.5)	0.217
Preoperative Cobb angle	0.9 (-1.0, 2.8)	0.330	1.9 (0.2, 3.6)	0.032
Surgery time in minutes	0.5 (-0.5, 1.5)	0.351	0.6 (-0.3, 1.5)	0.176
Anesthesia time in minutes	-0.3 (-1.1, 0.4)	0.379	-0.3 (-1.0, 0.3)	0.322
Pain score at activity on POD0	2.6 (-7.3, 12.4)	0.603	8.1 (-0.6, 16.9)	0.068

Table 5. Estimated effect sizes on the rank scale from the non-parametric ANCOVA of Liposomal Bupivacaine (LB) on VAS pain scores at rest on POD1 and POD2 as well as overall VAS pain scores adjusted for levels fused, preoperative Cobb angle, surgery duration, anesthesia duration, pain score at rest on POD0, and intraoperative morphine consumption. The coefficients represent adjusted differences in mean ranks between the LB and N-LB groups, or per unit increase in the covariates.

	VAS pain scores at rest on POD1		VAS pain scores at rest on POD2		Overall, VAS pain scores at rest	
	Effect size (95% C.I.)	P value	Effect size (95% C.I.)	P value	Effect size (95% C.I.)	P value
Liposomal Bupivacaine (LB)	-4.8 (-24.1, 14.6)	0.628	-42.3 (-62.2, -22.3)	< 0.001	-53.4 (-72.3, -34.4)	< 0.001
Intraoperative morphine consumption	-0.04 (-0.3, 0.3)	0.796	-0.1 (-0.4, 0.2)	0.419	-0.1 (-0.4, 0.2)	0.495
Levels fused	-2.0 (-7.3, 3.4)	0.468	0.4 (-5.0, 5.8)	0.874	-0.1 (-5.2, 5.1)	0.975
Preoperative Cobb angle	0.6 (-0.3, 1.5)	0.168	1.2 (0.4, 2.1)	0.006	1.1 (0.3, 1.9)	0.009
Surgery time in minutes	0.02 (-0.3, 0.4)	0.898	0.2 (-0.2, 0.6)	0.280	-0.03 (-0.4, 0.3)	0.894
Anesthesia time in minutes	-0.1 (-0.4, 0.2)	0.685	-0.2 (-0.5, 0.2)	0.369	-0.1 (-0.4, 0.2)	0.676
Pain score at rest on POD0	15.4 (11.1, 19.6)	< 0.001	9.0 (4.8, 13.3)	< 0.001	21.1 (17.1, 25.1)	< 0.001