Thoracic Epidural Anesthesia and Analgesia During the Perioperative Period of Thoracic Surgery: Levobupivacaine Versus Bupivacaine

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Objectives: **To compare the effects of thoracic epidural anesthesia with levobupivacaine or bupivacaine on block features, intraoperative hemodynamics, and postoperative analgesia for thoracic surgery.**

Design: **A prospective, randomized, and double-blind study.**

Setting: **A university hospital.**

Participants: **Fifty patients undergoing thoracic surgery.**

Interventions: **Patients received thoracic epidural catheterization either with levobupivacaine or bupivacaine. A bolus of 0.1 mL/kg of 0.25% levobupivacaine or 0.25% bupivacaine was administered, and infusion of the same drug with 0.25% concentration was started at 0.1 mL/kg/h. General anesthesia was induced after assessing the sensory block and maintained with 0.3% to 0.8% isoflurane and 50% O_2 in air. Epidural patient-controlled analgesia with the same agent was started at the end of the operation for 48 hours postoperatively.**

Measurements and Main Results: **Sensory block features such as onset time and spread were assessed for the next 20 minutes after the bolus dose. Heart rate and systolic, diastolic, and mean arterial blood pressures were recorded intraoperatively and postoperatively. Pain at rest and activity was evaluated by the visual analog scale (VAS) for 48 hours after the operation. All patients were comparable with respect to the demographic data. Onset time of the block and the number of blocked dermatomes and hemodynamic parameters were similar in both groups. All VAS assessments were comparable between groups except VAS at the 36th hour postoperative, which was higher in the levobupivacaine group ($p = 0.039$).**

Conclusions: **Thoracic epidural anesthesia with either levobupivacaine or bupivacaine provided comparable sensory block features, intraoperative hemodynamics, and postoperative analgesia for thoracic surgery.**

KEY WORDS: anesthetic techniques, thoracic epidural blockade, bupivacaine, levobupivacaine, thoracic surgery

THORACIC EPIDURAL ANESTHESIA and analgesia (TEAA) remains a preferred technique for the challenging and painful perioperative period of thoracic surgery.[1-3] TEAA with local anesthetics has been reported to benefit stable hemodynamics intraoperatively and lessen pulmonary complications postoperatively.[1-7] The efficient analgesia with TEAA also results in early mobilization, allowing painless ventilation and decreased morbidity and mortality.[2,8] Although there is a general consensus regarding the efficacy and utility of epidural analgesia for post-thoracotomy pain, there exists a controversy about the potential adverse effects of concentrated local anesthetic before the induction of general anesthesia when the epidural should be used as a major component of anesthesia management for lung resection. Some of these effects may include postoperative motor blockade and the propensity for autonomic blockade, leading to increased fluid requirements when a high concentration of local anesthetic is administered.

The most commonly used local anesthetic for perioperative TEAA is bupivacaine.[5,9] Because of the reported seizure and cardiac arrest events in patients after unintentional intravenous or overdose administration of bupivacaine, levobupivacaine, the pure S(−) isomer of bupivacaine, has gained popularity with fewer cardiovascular or central nervous system side effects.[5,10,11] However, in clinical practice, some studies evaluated the potency of levobupivacaine and its clinical features in comparison to bupivacaine for blocks other than thoracic epidurals.[12-16] Although the use of levobupivacaine for postoperative pain after thoracotomies has been reported,[5,17,18] to the authors' knowledge there is no reported study of TEAA comparing the effects of levobupivacaine and bupivacaine during the whole perioperative period of lung surgery requiring thoracotomy.

In this prospective, randomized, double-blind study, the authors aimed to compare the clinical features of commercially available solutions of bupivacaine and levobupivacaine including acute nerve-blocking properties, onset time and spread of the sensorial blockade, intraoperative cardiovascular effects, and postoperative analgesic efficacy during TEAA for thoracic surgery.

METHODS

After institutional ethics committee approval and patients' informed consent, 50 patients, older than 18 and American Society of Anesthesiologists physical status I to III, scheduled for elective thoracic surgery, were included in this prospective, randomized, and double-blind clinical study. The patients with uncontrolled hypertension; cardiac valvular diseases; unstable angina pectoris; or cardiac, hepatic, or renal failure and patients who had contraindications for epidural block such as coagulopathy or infection at the block site were excluded from the study. Also, patients with difficulty in cooperation and known allergy to study drugs were not enrolled in the study.

After obtaining demographic data including age, sex, body weight, and height, the patients were enrolled randomly into 2 groups to receive intraoperative TEAA with bupivacaine or levobupivacaine. The allocation of patients into groups was performed according to a random numbers list.

Before the induction of anesthesia, all patients were monitored with an electrocardiogram, pulse oximetry, and invasive blood pressure, and received 2 mg of midazolam intravenously. A 20-G epidural catheter was placed through an 18-G Tuohy needle using the median approach at T4-5 or T5-6 interspaces identified by the loss-of-resistance technique with saline. After insertion of the catheter a distance of 3 cm, a test dose of 60 mg of lidocaine and 1:200,000 of epinephrine was used

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Presented at the XXVII Annual ESRA Congress, September 24-27, 2008, Genoa, Italy.

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1053-0770/2503-0011$36.00/0
doi:10.1053/j.jvca.2010.07.017

Table 1. Demographic Data of the Patients and the Surgical Duration (Mean ± Standard Deviation)

	Group L	Group B	*p* Values
Age (y)	48.32 ± 13.54	44.96 ± 15.58	0.42
Weight (kg)	69.12 ± 9.76	70.28 ± 11.43	0.70
Height (cm)	168 ± 8.78	166 ± 8.74	0.42
Sex (M/F)	22/3	20/5	0.35
ASA (I/II/III) (number of patients)	5/12/8	5/14/6	0.80

Abbreviations: M, male; F, female; ASA, American Society of Anesthesiologists.

to detect misplacement in the intrathecal or intravascular space. After confirming the catheter placement, patients received an initial dose of 0.1 mL/kg of either 0.25% bupivacaine (group B) or 0.25% levobupivacaine (group L). Following the bolus dose of study drugs after epidural catheter insertion, block onset time was noted. The sensory block was assessed bilaterally with loss of pinprick sensation (with an 18-G needle)[19] at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, and 20 minutes after the bolus dose, and the number of bilaterally blocked dermatomes was recorded for the next 20 minutes. The authors also checked whether the epidurals still provided adequate sensory spread including surgical incision after the surgery during the postoperative period.

General anesthesia was induced with 5 to 7 mg/kg of thiopental, 1 μg/kg of fentanyl, 0.1 mg/kg of vecuronium and was maintained with 0.3% to 0.8% end-tidal isoflurane and 50% O_2 in air. The epidural infusion of the study drug with 0.25% concentration was initiated at 0.1 mL/kg/h along with the general anesthesia induction. Intraoperatively, an increase more than 20% in heart rate or systolic arterial pressure was treated with fentanyl (0.3 μg/kg), and a similar decrease in heart rate or systolic arterial pressure was treated with the adjustment of isoflurane concentration. All patients were to be extubated immediately after the surgery in the operating room before transport to the intensive care unit where they would stay for 24 hours before admission to the ward.

All patients underwent thoracotomies for pulmonary resections in the lateral decubitus position by the same surgeon and required one-lung ventilation. For the surgical technique, after the skin and subcutaneous incision posterolaterally, the latissimus dorsi muscle was completely divided, whereas the serratus anterior muscle was spared. The 5th or 6th intercostal spaces were preferred to enter the thorax.

At the end of the surgery, epidural patient-controlled analgesia (PCA) (Pain Management Provider, Serial No. 96456428; Abbot Laboratories, North Chicago, IL) with the same study drug was started as follows: a 0.125% concentration, a 4-mL/h infusion, a 2-mL bolus, 20 minutes lockout, and no limit for 4 hours for 48 hours postoperatively. Add-on therapy was planned with 1 g of paracetamol and 20 mg of tenoxicam every 8 hours intravenously. Rescue analgesics allowed to be administered twice were fentanyl, 0.3 μg/kg intravenously, for the first 24 hours and tramadol, 50 mg orally, between 24 and 48 hours postoperatively when the patient's verbal analog score (VAS) for pain was higher than 3.

Heart rate; systolic, diastolic, and mean arterial blood pressures; and peripheral oxygen saturation of the patients were recorded every 5 minutes throughout the study period, intraoperatively, and for 48 hours postoperatively. Pain scores at rest (VASr) and movement (VASm) were assessed by an 11-point verbal analog scale for pain (0 = no pain and 10 = the most severe pain) after the operation at 30 minutes and 1, 2, 4, 6, 12, 18, 24, 36, and 48 hours. VASm was evaluated during coughing in each patient to standardize the evoked pain for thoracic surgery. VAS score assessment was performed by the same observer throughout the study period. The total amount of study drug received by the patient, the ratio of PCA bolus, demand doses, and rescue

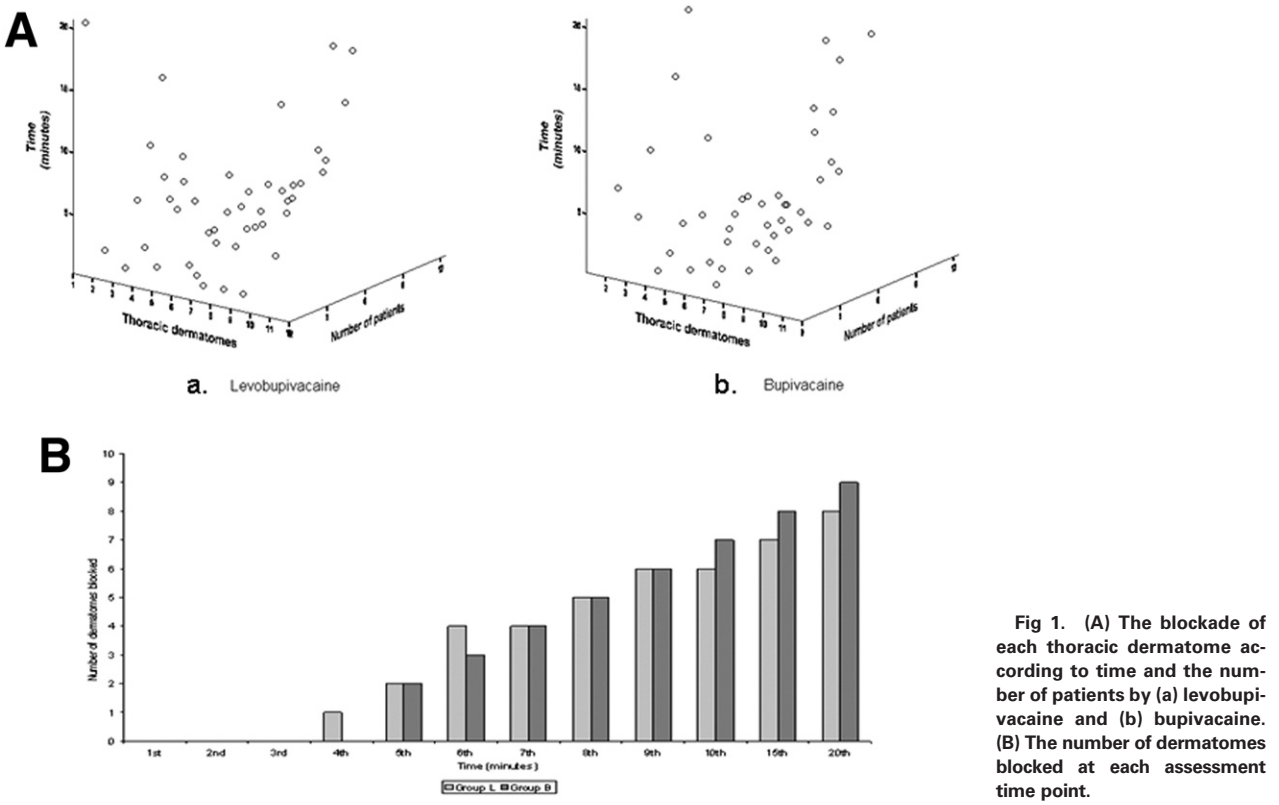

Fig 1. (A) The blockade of each thoracic dermatome according to time and the number of patients by (a) levobupivacaine and (b) bupivacaine. (B) The number of dermatomes blocked at each assessment time point.

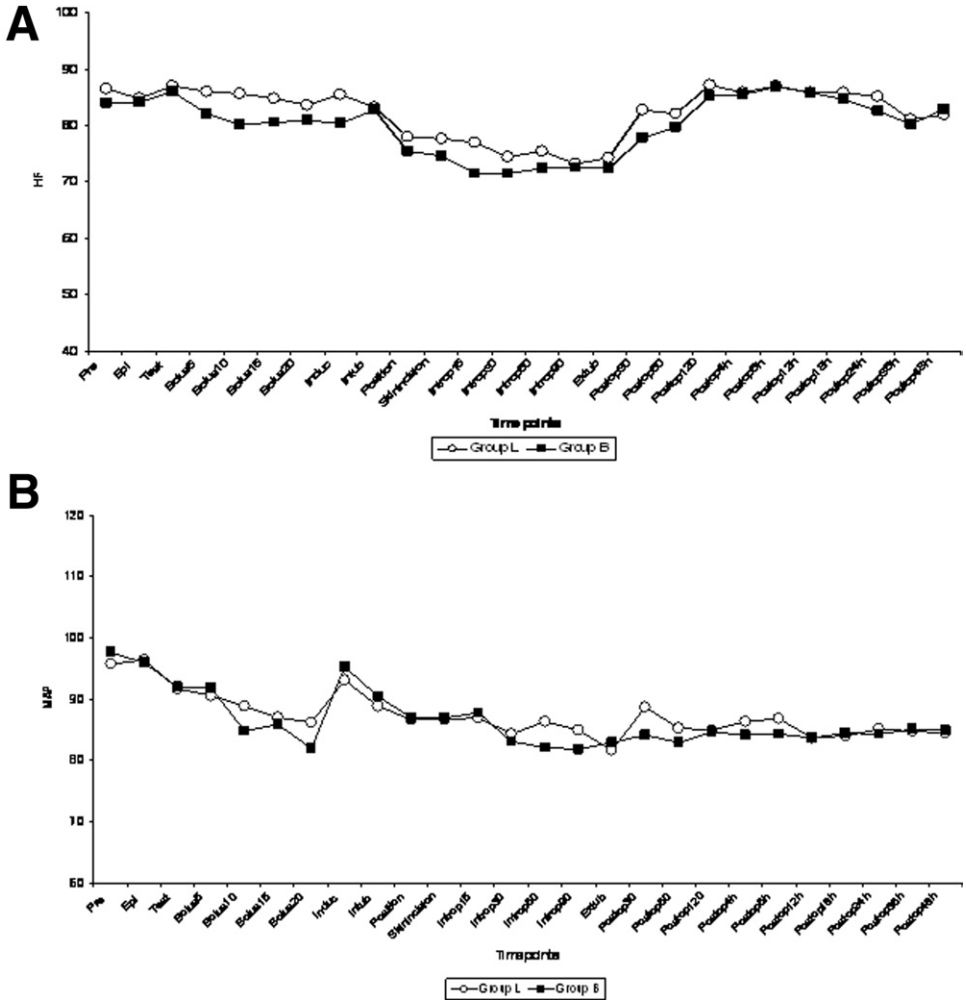

Fig 2. Hemodynamic data during the study period. (A) Heart rate (beat/min). (B) Mean arterial pressure (mmHg). HR, heart rate; MAP, mean arterial pressure; Pre, preoperative; Epi, after epidural catheter placement; test, after test dose; Bolus5, at 5 minutes after the bolus dose of the local anesthetic; Bolus10, at 10 minutes after the bolus dose of the local anesthetic; Bolus15, at 15 minutes after the bolus dose of the local anesthetic; Bolus20, at 20 minutes after the bolus dose of the local anesthetic; Induc, after the induction of general anesthesia; Intub, after intubation; Position, after positioning; Skinincision, after skin incision; Introp15, at 15 minutes intraoperatively; Introp30, at 30 minutes intraoperatively; Introp60, at 60 minutes intraoperatively; Introp90, at 90 minutes intraoperatively; Extub, after extubation; Postop30, at 30 minutes postoperatively; Postop60, at 60 minutes postoperatively; Postop120, at 120 minutes postoperatively; Postop4h, at 4 hours postoperatively; Postop6h, at 6 hours postoperatively; Postop12h, at 12 hours postoperatively; Postop18h, at 18 hours postoperatively; Postop24h, at 24 hours postoperatively; Postop36h, at 36 hours postoperatively; Postop48h, at 48 hours postoperatively.

analgesics were noted during the postoperative period. The study drugs were prepared by an anesthesia technician not involved in the study, and the data were recorded by an anesthesiologist blind to the study drug used. The anesthesiologist who administered the anesthesia also was blind to the study drugs throughout the entire study period including 48 hours postoperatively.

Data analysis was performed using SPSS (version 11.0; SPSS Inc, Chicago, IL). A power analysis indicated that 24 patients per group were required to detect a true difference of 2 dermatomes between the spread of the sensory blockade in the groups in which the anticipated standard deviation of the dermatomes was 2.4. The standard deviation was based on the total number of dermatomes blocked at the 20th minute of a pilot group of patients undergoing thoracotomy, exhibiting similar characteristics. The α error was set at 0.05, and the type-II error was set at 0.20; a p value less than 0.05 was considered as significant for all comparisons.

A Kolmogorov-Smirnov test was used to verify normal distribution inside groups. Categoric data were analyzed by the chi-square test. An independent sample t test was performed for between-groups comparisons. Data were presented as means with standard deviation or numbers (categoric variables). The number of dermatomes blocked after 20 minutes was given as the median, with the 25% to 75% interquartile ranges in parentheses.

RESULTS

Fifty patients were assigned to the study; 1 additional patient in each group was included for any protocol deviation. There was no statistical difference between the 2 groups in respect to the patients' demographic characteristics including age, sex, weight, height, and American Society of Anesthesiologists physical status (Table 1). Most of the patients were scheduled

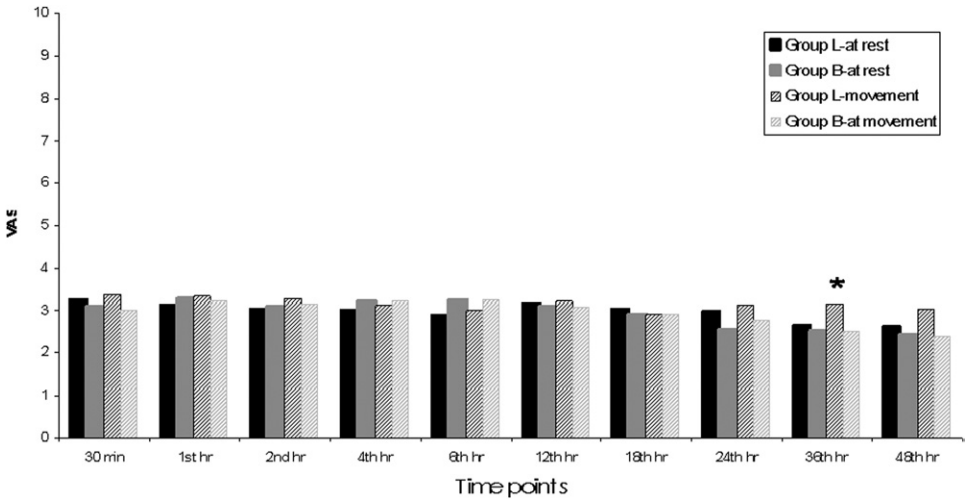

Fig 3. Pain scores at rest and movement for 48 hours postoperatively (*$p < 0.05$).

for thoracotomy because of malignancy (17 patients in group L and 19 patients in group B); the others were operated on because of infectious or benign cystic diseases.

The authors checked the level after test dose administration to ensure that it was actually in the epidural space, and the number of dermatomes blocked was similar in both groups (group L *v* group B, 1.8 ± 1.1 *v* 1.6 ± 0.7). Block-onset times (group L *v* group B, 4.8 ± 4.1 minutes *v* 4.8 ± 3.1 minutes, respectively) and the total number of dermatomes blocked after 20 minutes (group L *v* group B, 8 [7-9] *v* 9 [8-9], respectively) were similar. The blockade of each thoracic dermatome according to time in patients was comparable between groups (Fig 1A). The number of dermatomes blocked at each assessment time point (after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, and 20 minutes) was similar in both groups (Fig 1B).

There were no difference in intraoperative and postoperative hemodynamic parameters between groups at all assessment time points throughout the study period (Fig 2). The authors selected time points that might present significance and were concurrent with the time points of other parameters because cardiovascular parameters were recorded at 5-minute intervals. These time points were as follows: preoperative; after epidural catheter placement; after test dose; at 5, 10, 15, and 20 minutes after the bolus dose of the local anesthetic; after the induction of general anesthesia, intubation, positioning, and skin incision; at 15, 30, 60, and 90 minutes intraoperatively; after extubation; and at 30, 60, and 120 minutes and 4, 6, 12, 18, 24, 36, and 48 hours postoperatively. The authors preferred to present the mean arterial pressure to summarize arterial pressure; however, systolic and diastolic data also existed. None of the patients in the groups required increased fluid administration and vasopressor drug infusion.

All patients except 1 were extubated immediately after surgery in the operating room before transport to the intensive care unit, where every patient stayed for 24 hours before admission to the ward. One patient in the levobupivacaine group was extubated in the intensive care unit after 30 minutes because of late recovery from the muscle relaxant. However, none of the patients was reintubated.

One patient in group L and 2 in group B complained of nausea in the ward; 2 of them were treated with metoclopramide, and 1 patient in the bupivacaine group required ondansetron because she had resistant nausea followed by vomiting. All patients were discharged after 5.3 ± 0.9 (4-7) days in the ward. The discharge times were comparable between groups (group L *v* group B, 5.2 ± 1.0 *v* 5.4 ± 0.6, respectively). VAS assessments at rest and during activity were comparable between groups during the assessment period for 48 hours postoperatively, except for VASm at 36 hours postoperatively, which was higher in levobupivacaine group ($p = 0.039$) (Fig 3).

The total drug consumption, number of demands and boluses during PCA, and rescue analgesic requirements for 48 hours postoperatively were similar for 48 hours in the 2 groups (Table 2). In the first 24 hours, none of the patients in group B demanded additional analgesics, whereas 1 patient in group L required fentanyl administration once. One patient in each group required tramadol administration once on the ward during the 24- to 48-hour period.

DISCUSSION

TEAA has been favored for intraoperative and postoperative periods of thoracic surgery with its opioid-sparing effect.[1-3] TEAA with general anesthesia provides optimal perioperative conditions such as blunted cardiac response to surgical stress leading to stable hemodynamics, better ventilatory mechanics,

Table 2. Total Drug Consumption, Number of Demand, and Bolus Administrations During PCA for 48 Hours Postoperatively (Mean ± Standard Deviation)

	Group L	Group B	*p* Values
Number of demands	83.7 ± 29.3	83.4 ± 32.3	0.97
Number of bolus administrations	82.5 ± 29.4	80.6 ± 33.1	0.83
Total drug consumption (mg)	446.3 ± 73.6	441.6 ± 66.3	0.83

less hypoxemia, and decreased incidences of atelectasis and pulmonary infections.[1-6] Thus, TEAA with local anesthetics has been reported to improve pulmonary outcome.[4,7] Successful postoperative analgesia has been proven with TEAA, providing superior recovery after lung surgery.[2,8]

Bupivacaine has been the most commonly used long-acting local anesthetic; it has a safety margin between the dose required for clinical efficacy and the dose that brings out undesirable effects.[5,9,20] Bupivacaine and levobupivacaine have identical chemical and physical properties such as molecular weight, acid dissociation constant, liposolubility, partition coefficient, and protein binding; however, their isomeric contents, which provide unique interaction with biologic receptors, allow less toxicity with levobupivacaine.[21] The potency ratio between bupivacaine and levobupivacaine still is being debated.[5,11]

Levobupivacaine has been shown to be 2% less potent than bupivacaine, which was unlikely to have an effect in clinical practice.[12,20] However, the commercially available levobupivacaine has shown similar block features when administered in equal volume in milliliters to bupivacaine with the same concentration.[22] This may be explained by the fact that commercially available levobupivacaine actually has a 0.563% concentration of the molecule versus 0.5% in bupivacaine.[23] Because levobupivacaine contains 11% more of local anesthetic than 1 ampule of bupivacaine, the actual potency difference widens to approximately 13%.[13] The previous studies comparing levobupivacaine and bupivacaine with the same volume and concentration during epidural anesthesia reported a slower onset of motor blockade and a decreased quality of block with levobupivacaine; whereas the duration of motor and sensory blockade, the onset of sensory block, and the maximum upper spread were similar with levobupivacaine and bupivacaine.[24-26] In the present study, the authors showed that the onset and initial spread of sensory block were similar in each group. Levobupivacaine was reported to have a lower potency compared with bupivacaine in equal doses; however, the present authors administered both levobupivacaine and bupivacaine in doses calculated by milliliters per kilogram (body weight). This provided a 12.6% increase in the dose of levobupivacaine, which compensated for the potency difference between drugs, and this may explain comparable study parameters in both groups.

The potential effects of local anesthetics on cardiac contractility are related to nerve-blocking potencies of the agents. Bupivacaine is expected to exhibit more significant effects on cardiac indicators such as heart rate; and systolic, diastolic, and mean arterial pressure because the anesthetic potency of bupivacaine is higher than levobupivacaine. Furthermore, levobupivacaine has been reported to have significantly less effect on cardiovascular functions such as myocardial contractility and atrioventricular conduction than bupivacaine because bupivacaine has been reported to have a marked negative inotropic effect.[11,27] The cardiac effects of these drugs are more pronounced when administered intravasculary accidentally. However, in the present study, both levobupivacaine and bupivacaine provided comparable and clinically acceptable hemodynamic measurements throughout the perioperative period.

A main concern about thoracic surgery always has been the postoperative pain, which is considered to be a severe type of pain, and the widely used analgesia technique has been thoracic epidural blockade.[28] TEAA with local anesthetics throughout the perioperative period before the initiation of surgery and for 24 to 72 hours postoperatively has positive effects on the overall surgical period.[4,28] The use of levobupivacaine also has been reported in previous studies for postoperative analgesia with infusions or patient-controlled epidural top ups[29,30]; and both levobupivacaine and bupivacaine provided comparable and adequate pain relief.[26] In the present study, the patients were cared for with postoperative analgesia using the PCA technique by thoracic epidural catheter and presented similar pain relief with both local anesthetic agents. However, a rescue-analgesic protocol was followed by the nurses on general wards when the patients complained of any further pain.

The current study was not designed for cost analysis. The approximate cost of every 20 mL of bupivacaine 0.5% and levobupivacaine 0.5% were €2.5 Euro and €6.5, respectively. This difference roughly leads to a 171% increase of the drug-based cost in the levobupivacaine group.

In practice, characteristics such as efficacy, safety, potential undesirable effects, and the cost of local anesthetics leads to the choice of agent for clinical use.[20] The potential of levobupivacaine for reducing the severity of toxic effects after an accidental intravenous administration or overdosage may be a reason to prefer it in comparison to bupivacaine because both levobupivacaine and bupivacaine provided similar nerve-blocking and hemodynamic characteristics in many regional anesthesia techniques.[20] However, because the current study was not designed to compare the safety issues, the authors cannot suggest the use of levobupivacaine for its presumed increased safety.

According to the present study results, the authors suggest that when administered in equal volumes for TEAA, levobupivacaine is comparable to bupivacaine in terms of block features, hemodynamics, and postoperative analgesia for thoracic surgery.

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