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Bupivacaine combined with morphine for patient-controlled epidural analgesia after thoracotomy: high volume and low concentration *vs.* low volume and high concentration

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Abstract. – OBJECTIVE: In this prospective randomized controlled study, we aimed to evaluate the effects of the administration of equal doses of bupivacaine and morphine (BM) at high volume and low concentration (HV-LC) or low volume and high concentration (LV-HC) on the number of drugs consumed, pain scores and side effects.

PATIENTS AND METHODS: We randomized 64 patients who underwent thoracotomy into two groups. Group 1 received a solution prepared with 0.12% bupivacaine and 0.05 mg/cc morphine, administered with a basal infusion rate of 4 cc/h, a 2-cc bolus dose, and a 30-minute lockout time. Group 2 received a solution prepared with 0.48% bupivacaine and 0.2 mg/cc morphine, administered with a basal infusion rate of 1 cc/h, a 0.5-cc bolus dose, and a 30-minute lockout time. We compared patient-controlled epidural analgesia (PCEA) usage doses, pain scores, sensory and motor block, hemodynamic effects, side effects, and patient satisfaction in the postoperative periods.

RESULTS: An increase in drug consumption with PCEA was found in the first 24 hours postoperatively in Group 2 ($p<0.05$). Resting visual analog scale (VAS) scores were statistically significantly higher at hours 2, 28, 32, 36, 44 and coughing VAS scores were also higher at hours 2 and 20 in Group 2. Heart rates in Group 2 were lower than in Group 1 at hours 16, 24, 44 and 48 ($p<0.05$). The cephalic spread of the sensory block in Group 1 was more extensive ($p<0.05$). The groups demonstrated no significant differences regarding side effects and patient satisfaction ($p>0.05$).

CONCLUSIONS: The HV-LC approach resulted in better analgesia, less drug consumption, and greater cephalic spread of sensory block than the LV-HC approach. Both applications were effective and safe in terms of analgesia and side effects.

Key Words:

Anaesthetic techniques, Epidural, Postoperative pain, Thoracic surgery, Local anesthetic opioid combination, Sensory block, Patient-controlled analgesia.

Abbreviations

BM: bupivacaine and morphine, DBP: diastolic blood pressure, HR: heart rate, HV-LC: high volume-low concentration, iv: intravenously, LA: local anesthetics, LV-HC: low volume-high concentration, MABP: mean arterial blood pressure, PCA: patient-controlled analgesia, PCEA: patient-controlled epidural analgesia, RR: respiratory rate, SBP: systolic blood pressure, SD: standard deviation, SpO_2: peripheral oxygen saturation, VAS: visual analog scale, V/C: volume/concentration.

Introduction

A posterolateral thoracotomy is the standard approach for pulmonary operations. However, this incision is associated with severe postoperative pain, which can negatively affect pulmonary function[1]. Epidural analgesia provides effective pain relief after thoracotomy[2-4]. Combining opioids and local anesthetics (LAs) has been shown[5] to produce a synergistic anti-nociceptive effect in epidural analgesia. Such combinations allow lower doses of both drug groups while reducing the potential side effects of these drugs, which have various side effect profiles[6-8].

The relative effects of dose, volume and concentration of LA solutions are still not fully understood. Bromage[9] showed that the total dose of local anesthetic, rather than the volume, determines sensory block spread and analgesic quality. Studies[10-16] on the use of combinations of LAs and opioids have yielded contradictory results compared to those on the use of LAs alone. Studies evaluating the effects of various volumes and concentrations of the agents administered using the patient-controlled epidural analgesia (PCEA) method are limited. PCEA trials[11,13] involving patients undergoing lower abdominal surgery and gynecological surgery[14] have demonstrated that

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PCEA is safe and does not result in excessive sensory block. Whiteside et al[14] showed that the high volume, low concentration (HV-LC) approach to PCEA reduced drug consumption.

Few studies[15,17,18] have been conducted on the dosage, volume and concentration effects of LA and opioid combinations in thoracic surgery. The optimal LA-opioid combination has not yet been determined. Adding morphine to epidurally administered bupivacaine has been shown[19] to produce better analgesia than bupivacaine alone.

In our study, we aimed to compare the 24-hour consumption of bupivacaine and morphine (BM) administered at a high volume and a low concentration (HV-LC) to that of the same combination administered at a low volume and a high concentration (LV-HC) with PCEA. Additionally, we evaluated pain scores, sensory block, additional analgesic consumption, hemodynamic effects, side effects, patient-controlled analgesia (PCA) total volume, bolus, demands and patient satisfaction with using PCEA for thoracotomy pain.

Patients and Methods

The study was initiated after being approved by the Ethics Committee of the Atatürk Chest Diseases Thoracic Surgery Training and Research Hospital (its new name is Ankara Atatürk Sanatoryum Training and Research Hospital) of the University of Health Sciences (decision number 158, dated 27/05/2009). The study complied with the Declaration of Helsinki and was conducted after informed consent was obtained from all participants. Sixty-four patients aged 18-75 years with American Society of Anesthesiologists (ASA) scores of 1-3 who were scheduled for elective thoracotomy participated in the study and were divided into two groups. The sealed envelope method was used for randomization. Patients with significant endocrine/metabolic disorders, coronary artery disease, congestive heart failure, psychiatric disorders, bronchial asthma, chronic pain, a history of analgesic use, allergies to opioids or LA, contraindications to regional anesthesia (local infection and coagulopathy), those who rejected epidural catheterization, those with lesions due to trauma or metastasis in the thoracic vertebrae and those who could not cooperate with the use of the PCA device were excluded from the study.

At a visit the day before their operation, each patient was informed about the study and the visual analogue scale (VAS) which would be used to assess postoperative pain while coughing and resting. Each patient underwent intramuscular administration of 0.07 mg/kg midazolam and 0.01 mg/kg atropine for premedication 30 min before the operation. Electrocardiography, peripheral oxygen saturation (SpO_2) and non-invasive blood pressure and heart rate (HR) monitoring were performed in the operating room. Each patient received an infusion of 500 ml of crystalloid through a peripheral intravenous (IV) catheter. The patients were seated for epidural catheterization, and then skin asepsis and draping were performed. After prilocaine (2%, 60 mg) was applied, the catheter was placed through the T4-7 intervertebral spaces using the hanging drop technique. After catheter placement, each patient received a test dose of 3 cc (60 mg) of 2% lidocaine and 5 mcg/ml adrenaline (1/200,000).

All patients received 0.1 ml/kg of 0.250% bupivacaine through their epidural catheters before their surgical incisions and while their thoraxes were closed. We assessed bilateral sensory blockade with a pinprick test, whereas motor blockade was evaluated using the Bromage scale. Anesthesia was induced using 2 mg/kg of propofol, 0.1 mg/kg of vecuronium bromide and 1-1.5 mcg/kg of fentanyl. Anesthesia was maintained using 1-2% sevoflurane in a mixture of 50% air and 50% O2 and 0.03 mg/kg vecuronium bromide. During anesthesia, all patients were intubated with a double-lumen tube after induction. The patients were monitored with a pulse oximeter, an electrocardiograph, an arterial catheter, a central venous catheter, urine output (measured manually each hour) and a capnograph. The tube's placement was confirmed using fiberoptic bronchoscopy before each patient was shifted into the lateral decubitus position. A standard lung-protective ventilation protocol was applied to all patients when switching to single-lung ventilation. If a patient's HR increased by 30% or more from the baseline and their mean arterial blood pressure (MABP) increased by 20% or more from the baseline, 50-100 mcg of fentanyl was administered during the operation. The level of epidural catheter insertion, duration of surgery, time of thoracic closure and amount of fentanyl used during the operation were recorded for each patient. Crystalloid or colloid fluid was infused if the MABP decreased by 20% or more during the operation. If there was no response, the patient underwent IV administration of ephedrine (5 mg). If a patient's HR dropped below 50 beats/min, IV atropine sulphate (0.5 mg) was

administered. At the end of the operation, the neuromuscular blockade was reversed using IV administration of 0.03 mg/kg of neostigmine and 0.5 mg of atropine sulphate. After extubation, the patients were transferred to the surgical intensive care unit. During the postoperative period, a decrease in systolic blood pressure (SBP) of 20% or more from baseline or an SBP value lower than 90 mm Hg was defined as hypotension.

When each patient regained consciousness (cooperative), postoperative pain treatment began with solutions prepared for PCEA according to randomization. In the HV-LC group (Group 1, n=32), a solution prepared with 0.12% bupivacaine and 0.05 mg/cc morphine was administered *via* PCEA with a basal infusion rate of 4 cc/h, a 2-cc bolus and a 30-min lockout time. This solution consisted of 5 mg (1 cc) of morphine, 24 cc of 0.5% bupivacaine and 75 cc of saline.

The LV-HC group (Group 2, n=32) received a solution prepared with 0.48% bupivacaine and 0.2 mg/cc of morphine *via* PCEA with a basal infusion rate of 1 cc/h, a 0.5-cc bolus and a 30-min lockout time. This solution comprised 20 mg of morphine (2 cc), 96 cc of 0.5% bupivacaine and 2 cc of saline.

Thus, these solutions at two different concentrations were administered to both groups in equal doses of bupivacaine (9.6 mg/h) and morphine (0.4 mg/h).

The pain was evaluated using a 10-point (0=no pain and 10=unbearable pain) VAS. Motor block was assessed according to a modified Bromage scale (0=no motor block, 1=inability to raise legs, 2=inability to flex knees, and 3=inability to flex ankle joints). The patients' sedation levels were evaluated using the Ramsay Sedation Scale (1=anxious, agitated and restless; 2=cooperative, oriented and tranquil; 3=responsive to commands only and prone to sleep; 4=sleeping but responds quickly to a light glabellar tap or a loud auditory stimulus; 5=sleeping but responds slowly to a light glabellar tap or a loud auditory stimulus; 6=sleeping and produces no response to a light glabellar tap or loud auditory stimulus).

If patients experienced nausea and vomiting, they received IV metoclopramide. If the postoperative follow-up revealed inadequate analgesia (VAS>4), they received two doses of metamizole (500 mg each). If adequate analgesia was still not achieved, the patients received an additional 50 mg of tramadol. The patients' satisfaction with their analgesic treatment was evaluated using a four-point satisfaction scale (1=not satisfied at all, 2=not satisfied, 3=satisfied and 4=very satisfied) during the postoperative period. Before and after the start of treatment *via* the epidural catheter, at 30 min and at hours 1, 2, 6, 12, 16, 24, 28, 32, 36, 40, 44 and 48, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), sedation score, SpO_2 and VAS scores at rest and when coughing were evaluated and recorded. Metamizole and tramadol requirements (VAS>4) and cephalic and caudal block levels showing the distribution of sensory block were also evaluated and recorded.

The pinprick test was used for sensory block evaluation. Patient-controlled analgesia (PCA) total volume, PCA demand, PCA bolus doses, sedation score, and the Bromage scale score were recorded, as were occurrences of side effects such as nausea, vomiting, dizziness, dry mouth, itching, rash, constipation, headache, shoulder pain, respiratory depression, hypoxia and hypotension. Instances of patients receiving ephedrine and metoclopramide were recorded as well. Respiratory depression was defined as a RR of fewer than 10 breaths/min and SpO_2 of less than 90%. After each patient spent one night in the intensive care unit, their arterial line was removed, and invasive arterial pressure monitoring was terminated. Then, they were sent to the ward, where follow-up continued for up to 48 h.

Statistical Analysis

We used the SPSS package program (Version 22.0, SPSS Inc., Armonk, NY, USA) for statistical analysis of the data. We reported descriptive statistics as mean ± standard deviation (SD) or median (interquartile range) according to the normal distribution of continuous variables, and we provided descriptive statistics of categorical data in the forms of numbers and percentages. We evaluated the normality distribution of the data using the Kolmogorov-Smirnov test and the homogeneity of variances using Levene's test, whereas we used the Mann-Whitney U test to compare the non-normal numerical data and Student's *t*-test to compare the normal data. We used a Chi-squared or Fisher's exact test to evaluate the categorical data. We considered *p*-values lower than 0.05 as statistically significant.

We calculated the sample size for our study using the G*Power© software (version 3.1.9.2; Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). In our study, we aimed to calculate the sample size according to the 24-hour drug consumption amount, as was done in Whiteside et al[14] study. However,

the arithmetic mean and standard deviation values of the 24-hour values were not evaluated for the patient groups in Whiteside's study. Because no other similar studies had provided equivalent data for comparison, we conducted a pilot study including 10 individuals for our two patient groups. Based on the 24-h results of the patients in our pilot study, with a two-sided type I error of 0.05 and a power of 90% (1-β=0.9) and an effect size factor of 0.859, at least 30 subjects should have been included in each of our patient groups.

Results

We randomized 64 patients who were about to undergo posterolateral thoracotomy into two groups. Figure 1 shows the CONSORT flow diagram for our study. The two patient groups demonstrated no statistically significant differences in terms of demographic data, diagnosis, surgical type, operation time, ASA scores, intraoperative fentanyl consumption, or patient satisfaction (p>0.05; Table I). Moreover, they demonstrated no significant differences in terms of epidural insertion level (T4-T7) or thoracic closure times (p>0.05). The resting VAS score was statistically significantly higher in the LV-HC group (Group 2) than in the HV-LC group (Group 1) at hours 2, 28, 32, 36 and 44 (p<0.05; Table II). Group 2's cough VAS scores were statistically significantly higher than those of Group 1 at hours 2 and 20 (p<0.05, Table III). In Group 2, the SBP and DBP values at hour 40 were significantly lower than those in Group 1 (p<0.05). The same was noted for Group 2's HR values at hours 16, 24, 44 and 48 (p<0.05; Table IV). The RR value at hour 48 in Group 2 was significantly lower than that of Group 1 (p<0.05). No patient had an RR value lower than 10 rates/min. The groups demonstrated no significant difference in terms of SpO_2 (p>0.05). The PCA total volume, demands and boluses were compared between two groups at hours 1, 2, 6, 12, 24, 36 and 48. PCA total volume

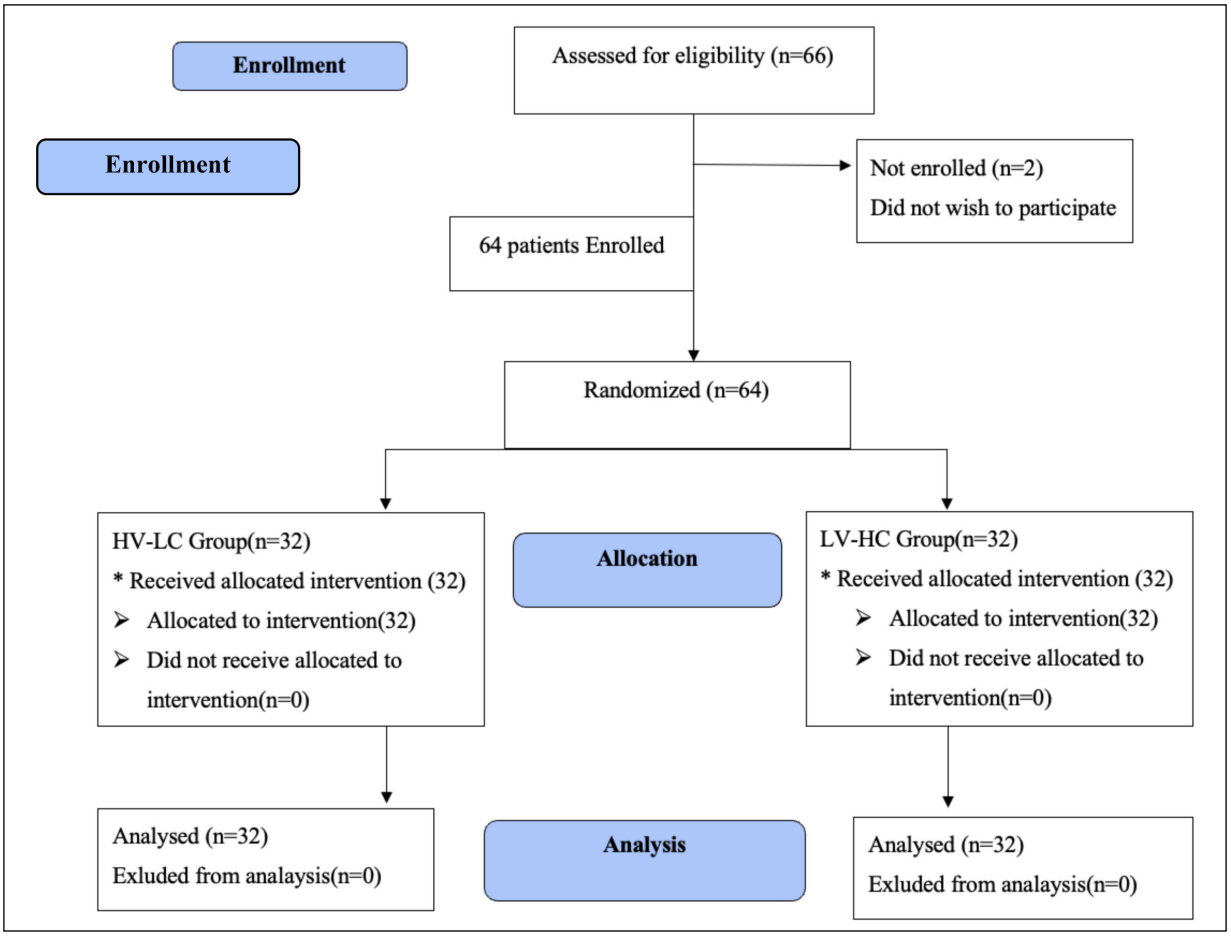

Figure 1. Flowchart of the patients. HV-LC: High volume-Low concentration, LV-HC: Low volume-high concentration.

Table I. Distribution of patients according to demographic characteristics, operation type, ASA, diagnosis and operation times, intraoperative fentanyl requirement, and patient satisfaction.

	Group 1	Group 2	*p*
Age$^{\beta}$ years, mean±SD	47.34±14.59	49.22±11.03	0.564
BMI$^{\beta}$ kg/m^2, mean±SD	24.33±3.43	23.50±3.66	0.349
Gender$^{\Phi}$, n (%)			
Female	26 (81.3%)	25 (78.1%)	0.756
Male	6 (18.8%)	7 (21.9%)	
Surgery$^{\Phi}$, n (%)			
Lobectomy	15 (46.9%)	15 (46.9%)	
Pneumonectomy	6 (18.8%)	6 (18.8%)	
Cystotomy	5 (15.6%)	5 (15.6%)	0.999
Ligation of Bullae	2 (6.3%)	2 (6.3%)	
Wedge Resection	2 (6.3%)	2 (6.3%)	
Decortication	2 (6.3%)	2 (6.3%)	
ASA$^{\Phi}$, n (%)			
1	-	4 (12.5%)	0.137
2	18 (56.3%)	17 (53.1%)	
3	14 (43.8%)	11 (34.4%)	
Diagnosis$^{\Phi}$, n (%)			
Lung Mass	18 (56.3%)	19 (59.4%)	
Bronchiectasis	5 (15.6%)	3 (9.4%)	0.999
Hydatid cyst	4 (12.5%)	5 (15.6%)	
Pneumothorax	2 (6.3%)	2 (6.3%)	
Pleural thickening	3 (9.4%)	3 (9.4%)	
Operation duration$^{\beta}$, minutes, mean±SD	168.13±40.99	163.13±48.61	0.754
İntraoperative Fentanyl$^{\beta}$, microgram, mean±SD	102.34±30.69	107.03±34.92	0.698
Satisfaction, Day 1$^{\beta}$, mean±SD	3.41±0.56	3.38±0.55	0.811
Satisfaction, Day 2$^{\beta}$, mean±SD	3.44±0.50	3.47±0.51	0.803

Continuous variables are expressed as the mean±standard deviation (SD) and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with a Student *t*-test $^{\beta}$ and categorical variables were compared using Pearson's Chi-square test or fisher exact test$^{\Phi}$. Statistically significant *p*-values are in bold. BMI: Body mass index. ASA: American Society of Anesthesiologist. $p<0.05$: Significant statistical difference among groups.

Table II. Comparison of groups based on Resting VAS scores.

	Group 1			Group 2			
Resting VAS	**Mean ± SD**	**Med (IQR)**		**Mean ± SD**	**Med (IQR)**		***p***
Baseline*	4.22±1.93	4.00	(2.00)	4.53±1.95	4.00	(3.00)	0.452
30 m*	3.28±1.55	3.00	(1.00)	3.75±1.65	4.00	(2.00)	0.093
1 h*	2.72±1.14	3.00	(1.00)	2.88±1.31	3.00	(1.00)	0.626
2 h*	2.06±1.05	2.00	(1.00)	2.84±0.99	3.00	(1.00)	**0.005**
6 h*	1.78±0.91	2.00	(1.00)	2.28±0.85	2.00	(1.00)	0.075
12 h*	1.59±0.87	2.00	(1.00)	2.06±1.52	2.00	(1.00)	0.302
16 h*	1.34±0.87	1.00	(1.00)	1.66±0.75	2.00	(1.00)	0.183
20 h*	1.09±0.96	1.00	(2.00)	1.34±0.79	1.00	(1.00)	0.138
24 h*	0.97±0.74	1.00	(0.50)	1.31±0.97	1.00	(1.00)	0.112
28 h*	0.84±0.77	1.00	(1.00)	1.38±1.10	1.00	(1.00)	**0.033**
32 h*	0.81±0.78	1.00	(1.00)	1.38±1.13	1.00	(1.00)	**0.018**
36 h*	0.78±0.87	1.00	(1.00)	1.31±0.97	1.00	(1.00)	**0.008**
40 h*	0.84±0.92	1.00	(1.00)	1.22±1.04	1.00	(1.00)	0.071
44 h*	0.66±0.79	0.50	(1.00)	1.13±0.83	1.00	(0.50)	**0.013**
48 h*	0.53±0.57	0.50	(1.00)	0.78±0.66	1.00	(1.00)	0.127

Continuous variables are expressed as the mean±standard deviation (SD) and median (interquartile range). Continuous variables were compared with the Mann-Whitney U test*. Statistically significant *p*-values are in bold. VAS: Visual analog scale. $p<0.05$: Significant statistical difference among groups.

Table III. Comparison of groups based on Cough VAS scores.

Cough VAS	Group 1			Group 2			p
	Mean ± SD	Med (IQR)		Mean ± SD	Med (IQR)		
Baseline*	4.41±2.01	4.00	(2.00)	4.69±2.16	4.00	(3.00)	0.579
30 m*	3.56±1.63	3.00	(1.50)	3.72±1.71	4.00	(2.50)	0.465
1 h*	2.94±1.22	3.00	(1.50)	3.00±1.39	3.00	(2.00)	0.899
2 h*	2.34±0.97	2.00	(1.00)	2.97±1.12	3.00	(2.00)	**0.029**
6h *	2.09±0.96	2.00	(1.00)	2.63±0.91	2.00	(1.00)	0.125
12 h*	1.88±1.18	2.00	(1.50)	2.23±0.92	2.00	(1.00)	0.483
16 h*	1.59±1.04	2.00	(1.00)	2.07±0.74	2.00	(0.00)	0.108
20 h*	1.25±1.08	1.00	(1.00)	1.69±0.90	2.00	(1.00)	**0.029**
24 h*	1.06±0.88	1.00	(1.00)	1.53±1.19	1.00	(1.00)	0.069
28 h*	1.22±1.21	1.00	(2.00)	1.53±0.95	1.00	(1.00)	0.119
32 h*	1.13±0.98	1.00	(2.00)	1.50±0.95	1.00	(1.00)	0.128
36 h*	1.13±1.16	1.00	(2.00)	1.38±1.04	1.00	(1.00)	0.239
40 h*	1.16±1.22	1.00	(2.00)	1.41±0.91	1.00	(1.00)	0.148
44 h*	1.00±0.92	1.00	(2.00)	1.19±0.82	1.00	(1.00)	0.321
48 h*	0.91±0.86	1.00	(1.50)	1.13±0.87	1.00	(1.50)	0.312

Continuous variables are expressed as the mean±standard deviation (SD) and median (interquartile range). Continuous variables were compared with the Mann-Whitney U test*. Statistically significant *p*-values are in bold. VAS: Visual analog scale. $p<0.05$: Significant statistical difference among groups.

was statistically significantly lower during all follow-up hours in Group 2 ($p<0.05$). In Group 2, both PCA demand and bolus number at hours 24, 36, and 48 were statistically significantly higher than in Group 1 ($p<0.05$; Table V).

BM consumption in the first 24 h was statistically significantly lower in Group 1 (bupivacaine 147.60±17.87 mg and morphine 6.15±0.74 mg) than in Group 2 (bupivacaine 162.45±25.47 mg and morphine 6.77±1.06; $p<0.05$; Table V). In the second 24-h period (hours 24-48), the groups demonstrated no statistically significant difference (Group 1: bupivacaine 137.10±17.46 mg and morphine 5.71±0.73 mg; Group 2: bupivacaine 145.20±22.11 mg and morphine 6.05±0.92 mg; $p>0.05$; Table V). Cephalic sensory block spread was statistically significantly higher in Group 1 than in Group 2 at 15 min, 30 min, 2 h, 6 h, 20 h, 24 h, 28 h, 32 h, 36 h, 40 h, 44 h and 48 h ($p<0.05$; Figure 2). Excess in this spread was around 0.5-1 segment when mean values were considered. The groups demonstrated no significant differences in terms of caudal extension ($p>0.05$; Figure 1). The groups demonstrated no significant difference in sedation levels ($p>0.05$). Neither motor block nor hypoxia was observed in either group ($p>0.05$). Hypotension and the related use of ephedrine were observed in two patients in Group 1, but the difference between the groups was not statistically significant ($p>0.05$). The groups demonstrated no significant difference in terms of the need for additional analgesics (metamizole and tramadol; $p>0.05$; Table VI). No significant difference was observed between groups regarding side effects such as nausea, vomiting, dizziness, dry mouth, itching, rash and constipation ($p>0.05$; Table VI). The percentages of patients requiring metoclopramide were 6.3% in Group 1 and 9.4%

Table IV. Comparison of groups based on heart rate changes.

HR	Group 1	Group 2	p
	Mean ± SD	Mean ± SD	
Baseline$^{\beta}$	72.56±13.33	67.53±12.26	0.110
30 m$^{\beta}$	73.84±13.90	71.41±14.36	0.795
1 h$^{\beta}$	74.81±13.13	73.91±14.56	0.271
2 h$^{\beta}$	81.25±13.51	77.59±12.81	0.064
6 h$^{\beta}$	86.81±10.46	81.13±13.47	0.141
12 h$^{\beta}$	89.03±10.23	84.75±12.63	0.174
16 h$^{\beta}$	93.00±13.36	88.38±13.54	**0.039**
20 h$^{\beta}$	96.66±11.87	89.53±15.03	0.067
24 h$^{\beta}$	92.59±11.99	87.19±11.22	**0.009**
28 h$^{\beta}$	93.41±12.50	85.91±9.49	0.209
32 h$^{\beta}$	90.66±10.78	87.44±9.46	0.285
36 h$^{\beta}$	89.66±11.01	86.91±9.32	0.451
40 h$^{\beta}$	90.63±12.84	86.94±7.57	0.300
44 h$^{\beta}$	91.75±11.32	86.28±7.32	**0.026**
48 h$^{\beta}$	91.69±12.63	85.28±6.28	**0.014**

Continuous variables are expressed as the mean±standard deviation (SD). Continuous variables were compared with a Student's *t*-test $^{\beta}$. Statistically significant *p*-values are in bold. $p<0.05$: Significant statistical difference among groups.

Table V. Comparison of groups based on patient-controlled analgesia demands, boluses and analgesic consumption.

	Group 1			Group 2			
PCA demands	**Mean ± SD**	**Med (IQR)**		**Mean ± SD**	**Med (IQR)**		***p***
1 h*	32.50±55.65	13.00	(17.00)	44.03±52.56	19.00	(72.50)	0.361
2 h*	60.84±106.88	20.50	(33.50)	68.16±73.02	33.00	(96.00)	0.271
6 h*	90.50±125.43	35.50	(97.00)	141.56±131.66	117.50	(189.50)	0.082
12 h*	104.47±146.47	39.50	(113.50)	159.81±154.15	97.50	(228.50)	0.112
24 h*	130.00±167.38	53.50	(133.50)	215.50±175.18	163.50	(282.50)	**0.012**
36 h*	152.03±178.18	69.00	(138.50)	259.31±213.78	171.50	(385.00)	**0.017**
48 h*	177.59±190.82	80.50	(245.50)	285.94±238.76	184.00	(420.00)	**0.027**
PCA boluses							
1 h*	1.88±0.34	2.00	(0.00)	1.78±0.42	2.00	(0.00)	0.324
2 h*	3.19±0.78	3.00	(1.00)	3.06±0.91	3.00	(1.50)	0.655
6 h*	6.25±2.76	5.50	(4.00)	7.88±3.66	8.00	(7.50)	0.059
12 h$^{\beta}$	8.72±4.06	8.00	(6.00)	11.66±5.86	12.00	(8.00)	**0.023**
24 h*	13.50±7.44	11.00	(10.50)	19.69±10.61	19.50	(17.00)	**0.019**
36 h$^{\beta}$	18.63±9.55	17.50	(16.50)	26.19±13.99	28.00	(22.00)	**0.014**
48 h$^{\beta}$	22.63±11.68	21.00	(17.00)	32.19±16.74	30.00	(23.50)	**0.010**
0-24 h							
Bupivacaine$^{\beta}$, mg	147.60±17.87	141.60	(25.20)	162.45±25.47	162.00	(40.80)	**0.019**
Morphine$^{\beta}$, mg	6.15±0.74	5.90	(1.05)	6.77±1.06	6.75	(1.70)	**0.019**
24-48 h							
Bupivacaine$^{\beta}$, mg	137.10±17.46	138.00	(24.00)	145.20±22.11	141.60	(25.20)	0.109
Morphine$^{\beta}$, mg	5.71±0.73	5.75	(1.00)	6.05±0.92	5.90	(1.05)	0.109

Continuous variables are expressed as the mean±standard deviation (SD), the median (interquartile range). Continuous variables were compared with the Student's *t*-test$^{\beta}$ or the Mann-Whitney U test*. Statistically significant *p*-values are in bold. PCA: Patient-controlled analgesia. $p<0.05$: Significant statistical difference among groups.

in Group 2, with no significant difference between the groups ($p>0.05$). The groups were similar regarding shoulder pain and related suprascapular block application ($p>0.05$).

Discussion

In our study, two different volumes and concentrations of equal doses of bupivacaine and morphine (BM) were administered *via* PCEA using an epidural catheter placed at the mid-thoracic level (T4-T7) in patients undergoing thoracic surgery. We investigated the dose, concentration, and volume effects of this combination, with our study's result showing that the quality of analgesia at rest was better in the HV-LC group on the first and second postoperative days. Additionally, cough VAS scores and BM combination consumption were lower in the HV-LC group than in the LV-HC group on the first postoperative day. Although the caudal spread was similar in the two groups, the cephalic spread was higher in the HV-LC group than in the LV-HC group. In the LV-HC group, although blood pressure and HR values were lower than those of the HV-LC at some measurement times, this change was not clinically significant, and the patients in both groups were hemodynamically stable.

A limited number of volume and concentration studies[15,17,18] on thoracic surgery have been conducted. Despite the existence of studies demonstrating that total dose is more effective in determining the quality of analgesia than LAs' volume and concentration, conflicting results have also been found. Laveaux et al[17] administered continuous thoracic epidural infusion with bupivacaine and sufentanil (0.5% bupivacaine and 4 mcg/ml of sufentanil; 1.5-2 ml/h) in the LV-HC group in thoracotomy cases in which a catheter was placed at a high epidural level. The authors compared this group with their HV-LC group (0.125% bupivacaine and 1 mcg/ml of sufentanil; 6-8 ml/h) and observed similar results in terms of analgesic effect (resting VAS), side effects and additional bolus requirements. These

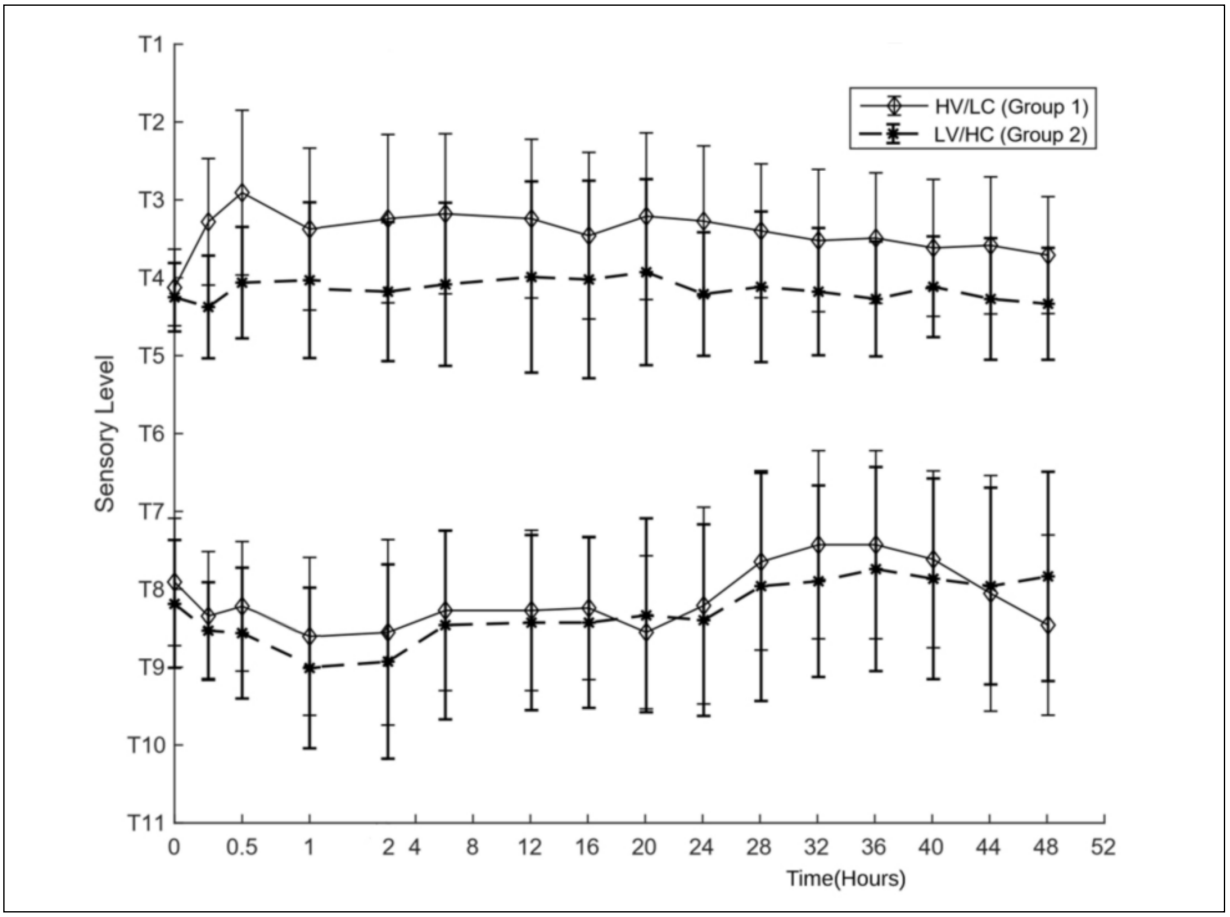

Figure 2. Mean cephalic and caudal sensory dermatomal levels in the two groups of patients during the 48-h study period. Cephalic sensory levels were higher in the low concentration group at 15 min, 30 min, 2 h, 6 h, 20 h, 24 h, 28 h, 32 h, 36 h, 40 h, 44 h, and 48 h time points ($p<0.05$). Caudal sensory levels were similar at all time points ($p>0.05$). HV-LC: High volume-Low concentration, LV-HC: Low volume-high concentration.

authors showed that the total drug dose is more important than the concentration or volume of an LA solution. Snijdelaar et al[15] reported that significantly more patients in their LV group required epidural bolus doses at rest on the first postoperative day, but their groups demonstrated no differences during exercise. The authors also showed that the number of patients with VAS scores above 4 was higher in the LV group (n=12) than in the HV group (n=6) on the first postoperative day, but this result was not statistically significant. Snijdelaar et al[15] found different results than Laveaux et al[17] despite using similar study protocols. They attributed the difference in their results to the small sample size and unequal patient distribution in Laveaux's study. Snijdelaar et al[15] also reported that the differences in the infusion doses applied in the LV group (0.75% bupivacaine and 4 mcg/ml of sufentanil; 1.0-1.3 ml/h) and the HV group (0.125% bupivacaine and 0.7 mcg/ml of sufentanil; 6-8 ml/h) may have changed the results.

In our study, LV patients' pain scores were higher at rest on the first and second postoperative days than those of our HV patients. Unlike Snijdelaar et al[15]'s study, the higher resting pain scores on the second postoperative day in our LV group may be attributed to the dose difference of continuously infused bupivacaine and the usage of various opioids.

Mendola et al[18] continuously infused a mixture of levobupivacaine and sufentanil *via* PCEA following thoracic surgery and allowed an epidural rescue bolus in situations in which a patient had a VAS score greater than 4 at a 1-h lockout. Their study, using three different concentrations of levobupivacaine, primarily evaluated side effects. The authors reported that their groups were similar in terms of pain scores and drug consumption. In Mendola's study[18], epidural infusion began before the patients were awakened. Moreover, all patients

Table VI. Postoperative side effects and additional drug requirements.

	Group 1		Group 2		
Side Effects	**n**	**(%)**	**n**	**(%)**	***p***
Nausea$^{\Phi}$	5	(15.6%)	4	(12.5%)	0.999
Vomiting$^{\Phi}$	2	(6.3%)	1	(3.1%)	0.999
Dizziness$^{\Phi}$	2	(6.3%)	1	(3.1%)	0.999
Dry Mouth$^{\Phi}$	3	(9.4%)	2	(6.3%)	0.999
Itching$^{\Phi}$	2	(6.3%)	1	(3.1%)	0.999
Rash	0	-	0	-	-
Constipation$^{\Phi}$	2	(6.3%)	2	(6.3%)	0.999
Headache	0	-	0	-	-
Hypoxia	0	-	0	-	-
Hypotension$^{\Phi}$	2	(6.3%)	0	-	0.492
Suprascapular block$^{\Phi}$	5	(15.6%)	2	(6.3%)	0.426
Presence of malignancy$^{\Phi}$	16	(51.6%)	17	(53.1%)	0.999
Mortality	0	-	0	-	-
Drug Requirements					
Metamizol					
500 mg	4	(12.5%)	8	(25.0%)	0.344
1,000 mg	12	(37.5%)	8	(25.0%)	
Tramadol$^{\Phi}$					
50 mg	7	(21.9%)	2	(6.3%)	0.086
100 mg	0	-	2	(6.3%)	
Ephedrine$^{\Phi}$	2	(6.3%)	0	-	0.492
Metoclopramide$^{\Phi}$	2	(6.3%)	3	(9.4%)	0.999

Categorical variables are expressed as either frequency or percentage. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test$^{\Phi}$. $p<0.05$: Significant statistical difference among groups.

received additional analgesics administered using a multimodal approach. Their applications might have masked analgesic differences resulting from volume and concentration properties.

Kunitoku et al[20] administered epidural bupivacaine (4.8 mg/kg) combined with fentanyl (12 mcg/kg) in patients undergoing gynecological laparotomy. They compared the LV-HC group (96 ml total volume and 2 ml/h of infusion rate) with the HV-LC group (240 ml total volume and 5 ml/h of infusion rate). The authors reported that their HV group had lower pain scores than those of their LV group on the first postoperative day. They did not find a significant difference between the groups in terms of the incidence of side effects. Similar to our study, Kunitoku et al[20] showed that increasing volume rather than concentration was most beneficial when equal doses were administered.

A few studies[13,14] have compared the effects of changing volume and concentration while maintaining equal doses in PCEA. Liu et al[13] administered, in lower abdominal surgery patients, a mixture of ropivacaine and fentanyl at three different concentrations for PCEA *via* an epidural catheter inserted at the T12-L1 level. Although similar analgesia was provided, more motor blockade was observed in the highest concentration group. This study showed that the concentration of ropivacaine solution was the primary determinant of motor blockade.

Whiteside et al[14] used the same combination after gynecological surgery *via* epidural catheterization at the T9-12 level. They observed a decrease in the doses used with PCEA in the first 24 h in the HV-LC group compared to the LV-HC group. Similarly, in our study, we found 24-hour epidural drug consumption to be lower in the HV-LC group.

Whiteside et al[14] applied equal doses at different volumes and concentrations, demonstrating the importance of volume and concentration in comparison with the total dose. They suggested that the therapeutic ratio of LA would be expanded if an HV-LC solution was used. The authors observed no significant difference between the groups concerning VAS scores. The higher VAS scores in the LV-HC group in our study may be because thoracotomy is more painful than gynecological surgery.

Existing PCEA studies[10,12] evaluating concentration have been conducted with opioid-free single levobupivacaine bolus applications or ropivacaine and fentanyl bolus applications[14]. In other studies[11,13], opioid-free levobupivacaine[11]

and ropivacaine and fentanyl mixtures have been administered using a bolus and background infusion[13]. It is challenging to compare these studies because they use different agents in different surgical groups. Two studies[11,14] have evaluated both the cephalic and caudal spread of the sensory block, revealing no difference among the groups in terms of the upper or lower sensory block levels.

Previous studies[21] have suggested, for theoretical reasons, that analgesia could be improved with the dilution of bupivacaine, a lipid-soluble LA. Administration of a bupivacaine dose in the HV-LC format may result in a more extensive sensory block due to the use of a larger solution volume. Compared to concentrated opioid solutions, diluted solutions may affect more opioid receptors with a more extensive anatomical spread[17,22]. Opioids also limit the regression of sensory block observed with LA alone and increase pain quality[11,13,14,17,22]. Morphine-induced cephalic spread may be greater[17,23]. In our study, the cephalic extension width was not clinically significant.

Some authors[12,24] have reported equal analgesia quality despite higher cephalic spread levels at the HV-LC group than at the LV-HC group. Postoperative multimodal analgesia applied to both groups in these studies may have masked the analgesic difference between the groups. These study results do not support Bromage's findings[9] that analgesic spread depended on the dose effect of the LA.

Sensory block primarily spreads caudally after high thoracic epidural injection, cephalically after lower thoracic injection and equal parts caudally and cephalically after mid-thoracic injection[25,26]. Although the same total dose of LA applied in different volumes causes a similar neural blockade spread, the intensity of the blockade can vary depending on the concentration[10,27]. Reports[25] on perioperative epidural analgesia with bupivacaine have shown that different patients had varying preferences for volume and concentration combinations in terms of analgesia. Additionally, in our study, both groups exhibited adequate analgesia and similarly sufficient levels of patient satisfaction. The differences between our two groups in terms of drug consumption and analgesia may also stem from differences in neural blockade intensity. According to the results found in the literature on the distribution of epidural blockade, especially in thoracic epidural analgesia, the total dose of LA seems to be the most crucial factor in determining the intensity of the sensory, sympathetic and motor neural blocks. However, contradictory study results are available[25,28,29]. Research[30] on PCEA shows that self-titrating analgesia allows most patients to achieve similar comfort levels despite differences in analgesic solutions. In our study, we anticipated that the effects on analgesia due to volume/concentration (V/C) differences could be demonstrated more clearly with the use of PCEA than with continuous epidural infusion. We chose the combination of bupivacaine and morphine because of its strong analgesic effect and low cost[31].

Bupivacaine is a long-acting amide-type LA. Its adverse cardiac effects have been found[32] to be related to its interaction with calcium channels and intracellular calcium influx and its effects on ATP synthesis in mitochondria. Its effects, such as ventricular arrhythmia and myocardial depression, are more significant than those of other LAs. Bupivacaine causes decreases in systolic and diastolic left ventricular function[33]. We observed no hemodynamically disturbing side effects at the doses used in our study. We observed hypotension, which was thought to be due to sympathetic block, in only two patients in the HV-LC group. The blood pressure and HR declines in the LV-HC group were within normal limits. This study has some limitations. We studied patients who underwent thoracotomy with high pain severity in a single center. The volume, concentration and dose effects of similar drug combinations may differ for treatment following various operation types. Additionally, such comparison studies may need to be conducted with larger numbers of patients to achieve more generalizable results.

Conclusions

This study showed that the BM combination with PCEA provided reduced drug consumption, better analgesia and higher cephalic sensory block in the HV-LC group than in the LV-HC group. Both groups achieved effective and safe analgesia, as well as similar results in terms of side effects and patient satisfaction.

Conflict of Interest

All authors declare that they have no conflict of interest.

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Gülay Ülger: resources and data curation.
Özgür Cirik: investigation and resources.
Ramazan Baldemi: formal analysis and data curation.
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Hilal Sazak: conceptualization and investigation.

Ethics Approval

The study was initiated after being approved by the Ethics Committee of the Atatürk Chest Diseases Thoracic Surgery Training and Research Hospital (its new name is Ankara Atatürk Sanatoryum Training and Research Hospital) of the University of Health Sciences (decision number 158, dated 27/05/2009). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration (as revised in 2013) and its later amendments or comparable ethical standards.

Informed Consent

The study complied with the Declaration of Helsinki and was conducted after informed consent was obtained from all participants.

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References

1) Hazelrigg SR, Landreneau RJ, Boley TM, Priesmeyer M, Schmaltz RA, Nawarawong W, Johnson JA, Walls JT, Curtis JJ. The effect of muscle-sparing versus standard posterolateral thoracotomy on pulmonary function, muscle strength, and postoperative pain. J Thorac Cardiovasc Surg Mar 1991; 101: 394-400.
2) Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology Mar 2006; 104: 594-600.
3) Tunç M, Çınar D, Şahin Ş, Sazak H, Köse SK. The effects of pre-emptive pregabalin on post-thoracotomy pain and epidural analgesia. Turk Gogus Kalp Dama 2014; 22: 129-137.
4) Barut GA, Tunç M, Şahin Ş, Ulus F, Sazak H. Effects of epidural morphine and levobupivacaine combination before incision and after incision and in the postoperative period on thoracotomy pain and stress response. Turk J Med Sci 2018; 48: 716-723.
5) Kaneko M, Saito Y, Kirihara Y, Collins JG, Kosaka Y. Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. Anesthesiology 1994; 80: 137-150.
6) Crews JC, Hord AH, Denson DD, Schatzman C. A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery. Anesth Analg Dec 1999; 89: 1504-1509.
7) Niemi G, Breivik H. Epidural fentanyl markedly improves thoracic epidural analgesia in a low-dose infusion of bupivacaine, adrenaline and fentanyl. A randomized, double-blind crossover study with and without fentanyl. Acta Anaesthesiol Scand 2001; 45: 221-232.
8) Frassanito L, Rodolà F, Concina G, Messina A, Chierichini A, Vergari A. The efficacy of the psoas compartment block versus the intrathecal combination of morphine, fentanyl and bupivacaine for postoperative analgesia after primary hip arthroplasty: a randomized single-blinded study. Eur Rev Med Pharmacol Sci 2008; 12: 117-122.
9) Bromage PR. Mechanism of action of extradural analgesia. Br J Anaesth 1975; 47 suppl: 199-211.
10) Dernedde M, Stadler M, Bardiau F, Boogaerts JG. Comparison of 2 concentrations of levobupivacaine in postoperative patient-controlled epidural analgesia. J Clin Anesth 2005; 17: 531-536.
11) Dernedde M, Stadler M, Taviaux N, Boogaerts JG. Postoperative patient-controlled thoracic epidural analgesia: importance of dose compared to volume or concentration. Anaesth Intensive Care 2008; 36: 814-821.
12) Dernedde M, Stadler M, Bardiau F, Seidel L, Boogaerts JG. Low vs. high concentration of levobupivacaine for post-operative epidural analgesia: influence of mode of delivery. Acta Anaesthesiol Scand 2006; 50: 613-621.
13) Liu SS, Moore JM, Luo AM, Trautman WJ, Carpenter RL. Comparison of three solutions of ropivacaine/fentanyl for postoperative patient-controlled epidural analgesia. Anesthesiology 1999; 90: 727-733.
14) Whiteside R, Jones D, Bignell S, Lang C, Lo SK. Epidural ropivacaine with fentanyl following major gynaecological surgery: the effect of volume and concentration on pain relief and motor impairment. Br J Anaesth 2000; 84: 720-724.
15) Snijdelaar DG, Hasenbos MA, van Egmond J, Wolff AP, Liem TH. High thoracic epidural sufentanil with bupivacaine: continuous infusion of high volume versus low volume. Anesth Analg 1994; 78: 490-494.
16) D'Ambrosio A, Spadaro S, Mirabella L, Natale C, Cotoia A, De Capraris A, Menga R, Salatto P, Malvasi A, Brizzi A, Tinelli A, Dambrosio M, Cinnella G. The anaesthetic and recovery profile of two concentrations (0.25% and 0.50%), of intrathecal isobaric levobupivacaine for combined spinal-epidural (CSE) anaesthesia in patients undergoing modified Stark method caesarean delivery:

a double blinded randomized trial. Eur Rev Med Pharmacol Sci 2013; 17: 3229-3236.

17) Laveaux MM, Hasenbos MA, Harbers JB, Liem T. Thoracic epidural bupivacaine plus sufentanil: high concentration/low volume versus low concentration/high volume. Reg Anesth 1993; 18: 39-43.

18) Mendola C, Ferrante D, Oldani E, Cammarota G, Cecci G, Vaschetto R, Della Corte F. Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. Br J Anaesth 2009; 102: 418-423.

19) Scott NB, Mogensen T, Bigler D, Lund C, Kehlet H. Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response. Br J Anaesth 1989; 62: 253-257.

20) Kunitoku Y, Sakaguchi H, Yano T, Ushijima K. [Low concentration/high volume is more effective than high concentration/low volume for postoperative continuous epidural analgesia with the combination of bupivacaine and fentanyl]. Masui 2001; 50: 20-24.

21) Slade JM. Epidural bupivacaine for aortic surgery. The effect of dilution on the quality of analgesia. Anaesthesia 1994; 49: 21-24.

22) Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2001; 1: 1-36.

23) Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology 1982; 56: 431-436.

24) Dernedde M, Stadler M, Bardiau F, Boogaerts J. Comparison of different concentrations of levobupivacaine for post-operative epidural analgesia. Acta Anaesthesiol Scand 2003; 47: 884-890.

25) Visser WA, Lee RA, Gielen MJ. Factors affecting the distribution of neural blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus thoracic epidural anesthesia. Anesth Analg 2008; 107: 708-721.

26) Visser WA, Liem TH, van Egmond J, Gielen MJ. Extension of sensory blockade after thoracic epidural administration of a test dose of lidocaine at three different levels. Anesth Analg 1998; 86: 332-335.

27) Sakura S, Sumi M, Kushizaki H, Saito Y, Kosaka Y. Concentration of lidocaine affects intensity of sensory block during lumbar epidural anesthesia. Anesth Analg 1999; 88: 123-127.

28) Kaçmaz O, Gülhaş N, Erdoğan Kayhan G, Durmuş M. Effects of different epidural initiation volumes on postoperative analgesia in cesarean section. Turk J Med Sci 17 2020; 50: 1955-1962.

29) Pathak A, Yadav N, Mohanty SN, Ratnani E, Sanjeev OP. Comparison of Three Different Concentrations 0.2%, 0.5%, and 0.75% Epidural Ropivacaine for Postoperative Analgesia in Lower Limb Orthopedic Surgery. Anesth Essays Res 2017; 11: 1022-1025.

30) Smith AJ, Haynes TK, Roberts DE, Harmer M. A comparison of opioid solutions for patient-controlled epidural analgesia. Anaesthesia 1996; 51: 1013-1017.

31) Valairucha S, Maboonvanon P, Napachoti T, Sirivanasandha B, Suraseranuvongse S. Cost-effectiveness of thoracic patient-controlled epidural analgesia using bupivacaine with fentanyl vs bupivacaine with morphine after thoracotomy and upper abdominal surgery. J Med Assoc Thai 2005; 88: 921-927.

32) Sztark F, Malgat M, Dabadie P, Mazat JP. Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochondrial bioenergetics. Anesthesiology 1998; 88: 1340-1349.

33) Knudsen K, Beckman Suurküla M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997; 78: 507-514.