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Original Article

The comparative study of epidural levobupivacaine and bupivacaine in major abdominal surgeries

Ali Uzuner[1], Kemal Tolga Saracoglu[2], Ayten Saracoglu[2], Ozcan Erdemli[3]

Abstract

BACKGROUND: Opioid and local anesthetic infusion by an epidural catheter is widely used as a postoperative pain management method after major abdominal surgeries. There are several agents nowadays to provide sufficient analgesia. The agents which cause less side effects but better quality of analgesia are more valuable. We aimed to postoperatively compare the analgesic, hemodynamic and arrhythmogenic effects of epidural levobupivacaine-fentanyl and bupivacaine-fentanyl solutions.

METHODS: Fifty patients were scheduled to undergo major abdominal surgery in this clinical trial. The parameters were recorded pre- and post-operatively. In Group I (n=25), bupivacaine with fentanyl solution and in Group II (n=25), levobupivacaine with fentanyl solution was infused via epidural patient-controlled analgesia (PCA). According to the preoperative and postoperative holter recording reports, the arrhythmogenic effects were examined in four catagories: ventricular arrhythmia (VA), supraventricular arrhythmia (SVA), atrioventricular conduction abnormalities and pauses longer than two seconds.

RESULTS: Mean visual analog scale (VAS) values of groups did not differ at all time. They were 6 at the end of the surgery (0. Min, p = 0.622). The scores were 5 in Group I and 4 in Group II in 30. min (p = 0.301). The frequency of SVA was higher in bupivacaine group.

CONCLUSIONS: The results of our study suggest that same concentration of epidural levobupivacaine and bupivacaine with fentanyl provide stable postoperative analgesia and both were found safe for the patients undergoing major abdominal surgery.

KEYWORDS: Epidural, Bupivacaine, Levobupivacaine, Analgesia, Abdominal Surgery.

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Today, the postoperative pain scores are lower by using multimodel analgesia and epidural patient-controlled analgesia (PCA).[1] As is known, insufficient pain therapy prolongs the hospital stay and rises the mortality rates.[2] PCA is commonly used for acute and chronic pain therapy by the placement of a catheter in epidural space or intrathecal area. Consequently, lower doses of drugs can be used and the side effects reduce. More effective analgesia and early mobilisation are the advantages.[3] PCA allows patients to control their own pain as small predetermined doses of analgesic medication within limits prescribed by their physician, resulting in pain relief and patient satisfaction.[4]

Local anesthetics inhibit the sodium channels on neural membranes. Therefore, they cause a loss of conduction on neural structure and a loss of sensorial innervation.

1- Anesthesiologist, Department of Anesthesiology and Reanimation, Alanya Education and Research Hospital, Antalya, Turkey.
2- Anesthesiologist, Department of Anesthesiology and Reanimation, School of Medicine, Marmara University of Medical Sciences, Istanbul, Turkey.
3- Associate Professor of Anesthesiology, Department of Anesthesiology and Reanimation, Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey.
Corresponding Author: Ayten Saracoglu
E-mail: aytentolgasaracoglu@mynet.com

Systemic toxicity results from excessive blood levels of local anesthetics in central nerve system and cardiovascular system when they are injected intravenous (IV) by mistake.[5] They cause directly negative inotrophy, myocardial conduction abnormalities and arrhythmias. Arrhythmogenic effects of these drugs are related with repolarisation of potassium, sodium and calcium channels.[6] Consequently with this mechanism, cardiac impulse conduction slows down, QRS complex widens, PR distance gets longer, atrioventricular block occurs and fatal ventricular arrhythmias such as ventricular tachicardy or ventricaular fibrilation occurs.[7]

Age, sex, psychological or pharmacological factors effect the postoperative pain scores. The type of surgery plays also an important role.[8] The pain therapy after abdominal and thoracal surgeries is adequately successfull by using epidural PCA.[9] There are several agents in this area but on the other side the hemodynamic and cardiac side effects restrict their use. Bupivacaine is a long-acting amide and widely used as local anesthetic for epidural anesthesia. It has a beneficial ratio of sensory to motor block in epidural anesthesia. This agent provides also high quality analgesia in the postoperative period. However bupivacaine-induced cardiotoxicity in patients following accidental intravascular injection limits its use.[10] It has also potential for neurotoxicity. Sudden cardiac arrests and high proportion of maternal deaths were reported.[11] Therefore, a local anesthetic which has similar effects as bupivacaine but has less side effects on cardiovascular system was needed. Bupivacaine is used as a racemic mixture of equimolar amounts of R(+)- and S(-)-bupivacaine. R(+)- bupivacaine is found more toxic to both the central nervous system and the cardiovascular system.[12] Levobupivacaine (S-1-butyl-2-piperidylformo-2′,6′-xylididehydrochloride) is the pure S(-)-enantiomer of racemic bupivacaine. Preclinical animal and volunteer studies showed less cardiac toxicity than bupivacaine.[13] It seems to be an alternative local anesthetic agent in epidural anesthesia.

Our goal in this prospective, double blind, randomized study was to compare the levobupivacaine-fentanyl solution with bupivacaine-fentanyl solution to determine the analgesic, hemodynamic and arrhythmogenic activity by recording VAS scores, arterial blood pressure and holter monitorisation.

Methods

After obtaining institutional ethical committee approval and written informed consent, 50 ASA physical status I-III patiets, aged from 30 to 75 years, undergoing elective major abdominal surgery were included in this prospective, randomized, double blind study. Patients with cardiac desease, uncontrolled hypertension, hypovolemia, cronically hepatic or renal disease, significant electrolyte disorder, restrictive or obstructive respiratory disease, acute intermittent porphyria, neurological disorder, bleeding or coagulation test abnormalities, diabetes, allergy to local anesthetics or opioids and psychological disorders were excluded. The patients were shedulded for general anesthesia. A 20 G epidural catheter was placed before anestesia induction. The anesthetists who performed the epidural catheterisation and collected the datas were blinded to the solutions. The patients were randomized into two groups by drawing of lots.

In Group I (n=25), 250 mg bupivacaine 0.5% and 400 µg fentanyl in 150 cc saline 0.9% and in Group II (n=25), 250 mg levobupivacaine 0.5% and 400 µg fentanyl in 150 cc saline 0.9% was infused via epidural PCA. The concentration of the solution was 0.125% for bupivacaine and levobupivacaine, 3 µ/ml for fentanyl as used in previous studies.[14,15] The device was consisted of a syringe pump and activated by a hand switch that delivered the demand dose of solution epidurally. Patients were informed to press the button when they felt pain. The instructions about PCA (Grasebay 3300),

holter mashines (Dms300-12L) and VAS scores were given during the preoperative patient visits. The holter mashine was applicated and started recording 24 hours before the operation.

The degree of motor blockade was assessed using the Modified Bromage Scale: 0 = free movement of legs and feet; 1 = inability to raise extended leg but able to move knees and feet 2 = unable to flex knees but with free movement of feet 3 = unable to move feet or knees.[16] Maximum cephalad sensory blockade to pinprick, cold and touch was measured. Pain scores were assessed by VAS. In this scale 0 would mean 'No pain' and 10 would mean 'Worst possible pain'. VAS values were recorded at 0, 1, 3, 5, 7, 11, 15, 19th and 23rd hour in the postoperative period. 0.25% bupivacaine in 10 ml for Group I and 0.25% levobupivacaine for Group II was injected via epidural catheter following the record of VAS value immediatly after the surgery in the recovery room. Then the infusion of epidural PCA was started. Infusion rate was set as 4 ml/h and bolus dose was set as 5 ml with lockout 20 minutes. When the VAS value of the patient was higher than 3, additional 5 ml bolus dose was given and recorded. The datas were compared as excessive analgesic requirement.

Before epidural catheterisation, a peripheral 18 G venous cannula was placed as precaution. Mean arterial blood pressure was measured at 5 minutes interval before and during the procedure. Pulse oxygen saturation and heart rate were recorded continuously. Using an aseptic technique, 18 G Tuohy needle was introduced in the midline at the lumbar 3-4 or 4-5 interspace with the patients undergoing low anterior resection for rectum cancer and at the thoracal 7-8 or 6-7 interspace with the patients undergoing total gastrectomy for stomach cancer. 20 G epidural catheter was settled via Tuohy cannula and 60 mg lidocaine test dose was performed. Then the patients were premedicated by 0.03 mg/kg intravenous (IV) midazolam. After completion of epidural block, anesthesia was induced with IV penthotal 5 mg/kg and IV fentanyl 3 µg/kg. Tracheal intubation was facilitated with rocuronium 0.6 mg/kg. Patients' lungs were mechanically ventilated with 65% nitrous oxide and 35% oxygen with a fresh gas flow of 5 lt/min. A heart rate under 45 beat/min was accepted as bradycardia and treated with atropine 0.5 mg IV. Mean arterial pressure under 50 mmHg was considered as hypotension and treated by 500 ml IV colloid infusion. If colloid did not rise the blood pressure, 10 mg IV ephedrine was administered.

The patients were again moniterized after the surgery in recovery room and the values of arterial systolic and diastolic pressure, heart rate, VAS, oxygen saturation and respiratory rates were recorded. The infusion of epidural solution has been started. The sedation scores were determined by Ramsay Sedation Scale:

1. Agitated or restless patient
2. Co-operative, oriented and tranquil patient
3. Responds to commands only
4. Brisk response to a light glabellar tap or auditory stimulus
5. Does not respond to mild prodding or shaking
6. Exhibits no response

The patients who were awake and hemodynamically stable were transported to intensive care unit (ICU). Patients were extubated when their blood gase values were in normal range. The recording of parameters were completed in the ICU until 23rd postoperative hour. Every patient had additionally 4 gr paracetamol per day for multimodal analgesia. Nausea and vomiting were treated by metoclopramid 10 mg IV and pruritus by difenhydramine 10 mg IV and were repeated as necessary.

Statistics

Statistical Package for Social Sciences (SPSS) for Windows programe (ver.10) was used for statistical analyses. Shapiro Wilk parametric test was used for comparisons between continuous variables. $P < 0.05$ was taken to be statistically significant. For categorical

variables, proportions of the variances in two groups were compared by the chi-square test. Measurements were compared by the Student's t-test for independent samples. Group size was selected using proportions sample size estimates ($\dot{\alpha} = 0.05$, $\beta = 0.09$).

Results

Fifty one patients who underwent major abdominal surgery were enrolled in the study. One patient in bupivacaine group was excluded from the analyses because of failure to perform the epidural blockade and the patient was treated with IV PCA. This left 25 patients in Group I. 16 female and 34 male patients were studied. Demographic data for each group was similar (Table 1). No significant difference was obtained in systolic or diastolic pressure values between groups (Figure 1). Thirty two patients (64%) underwent low anterior resection operation for rectum cancer and 18 (36%) patients underwent total gastrectomy for stomach cancer. Eleven patients who had low anterior resection and four patients who had total gastrectomy needed blood transfusion. Mean duration of surgery for rectum cancer and stomach cancer was 128 ± 21 min and 79 ± 12 min respectively. The data analysis showed that the incidence of pruritus was not clinically and statistically different in patients receiving epidural bupivacaine compared with patients receiving levobupivacaine ($p > 0.05$). Postoperative satisfaction with the epidural analgesia was similar with median scores of 69 (levobupivacaine) and 73 (bupivacaine) (VAS; 100 mm = extremely satisfied) in the first 24 hour after operation.

There was no significant difference between groups for heart rate (Figure 2), arterial oxygen saturation (Figure 3), VAS values (Figure 4) and postoperative analgesic requirements. Total analgesic consumption was 145 ml for group I and 150 ml for group II ($p = 0.091$). Additional analgesic need was 25 ml for Group I and 30 ml for Group II ($p = 0.185$). Supraventricular arrhythmia (SVA) incidence for the postoperative period was significantly higher in bupivacaine group ($p < 0.05$). Total number of PCA demands was 14 and 15 for Group I and Group II, respectively. Preoperative SVA was observed 4 times in both groups. However the incidence increased to 20 times in bupivacaine group and 9 times in levobupivacaine group. The type of supraventricular arrhythmias included atrial fibrillation (0%), atrial flutter (0%), paroxysmal supraventricular tachycardia (92%) and Wolf-Parkinson-White Syndrome (8%). Postoperative incidence of ventricular arrhythmia (VA), conduction abnormalities and pauses longer than two seconds were similar in both preoperative and postoperative period ($p > 0.05$). Additionally, the heart rate of patients in bupivacaine group increased during first postoperative three hours but this result was not statistically significant.

Two patients had hypotension (mean arterial pressure under 50 mmHg) after epidural catheterisation. They were treated with colloid infusion but one of them needed 10 mg ephedrine after liquid infusion. None of the patients had bradycardia during the procedure. All patients were intubated successfully on first attempt. There were no difficult intubations or deaths. There were no

Table 1. Demographic characteristics

	Group I	Group II
Age	58.2 ± 11.75	60.6 ± 14.07
Female	9 (%36.0)	7 (%28.0)
Male	16 (%64.0)	18 (%72.0)
Weight	67.8 ± 8.26	68.8 ± 11.22

Group I: 0.125% bupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. Group II: 0.125% levobupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. $p>0.05$

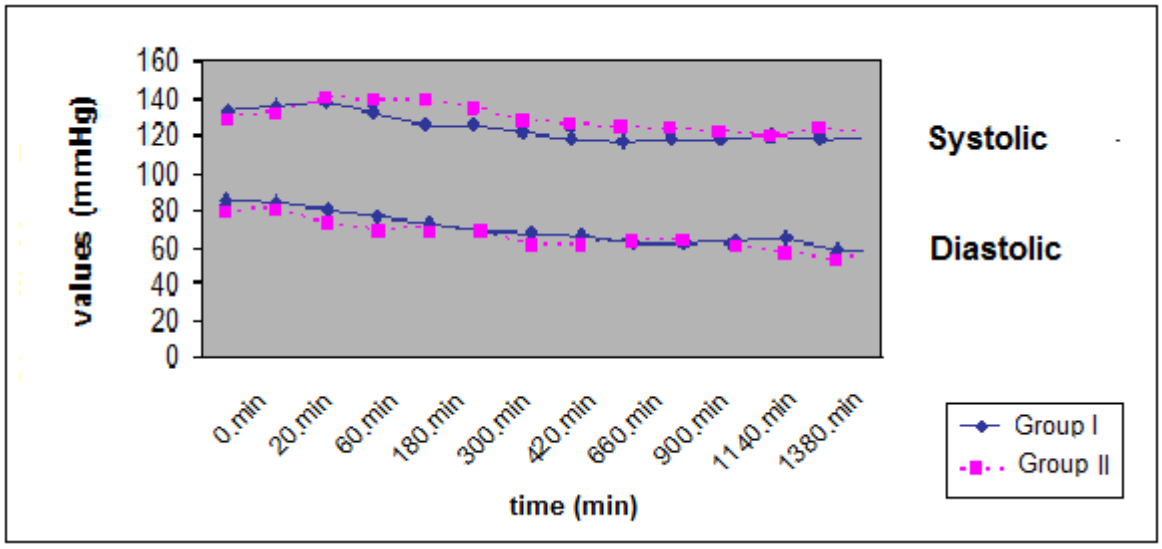

Figure 1. Systolic and diastolic arterial pressure
Group I: 0.125% bupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. Group II: 0.125% levobupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. $p > 0.05$

major anesthetic or surgical complications. There were no clinically meaningful differences between treatment groups in physical findings or laboratory parameters. The levels of sensory and motor block did not differ among groups at all time. Bromage scores (n, 0/1/2/3) of Group I were 21/4/0/0 patients and of Group II were 22/3/0/0 patients. ASA categorization (n, 1/2/3) of Group I was 15/6/4 and of Group II was 12/8/5 patients. No cases of cardiac depression or central nervous system toxicity caused by vascular absorption or direct intravascular injection of local anesthetic

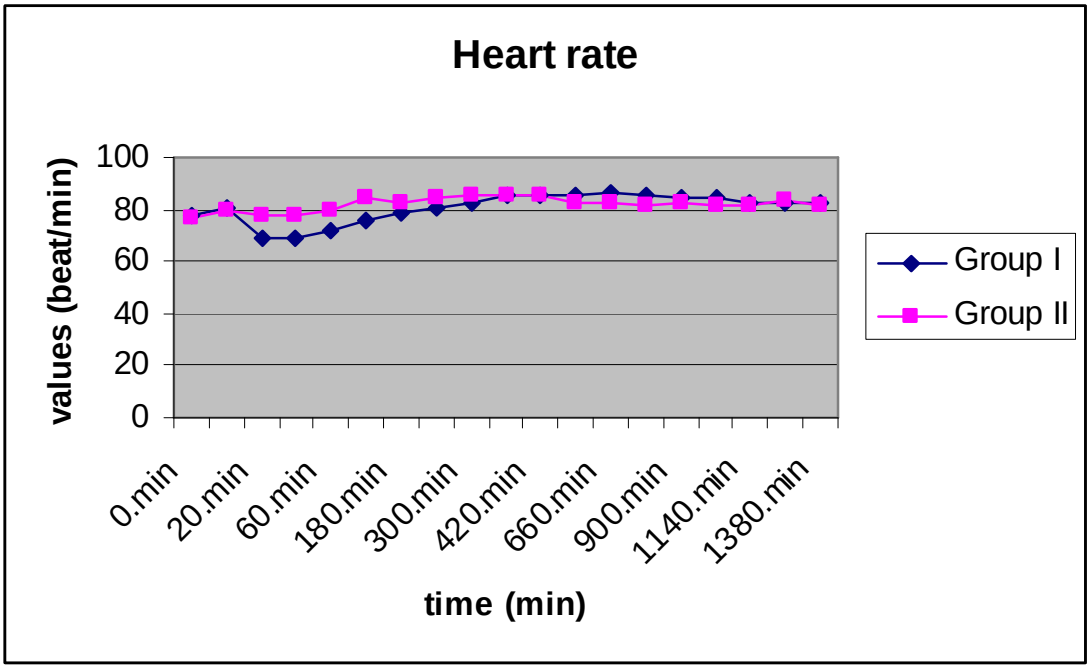

Figure 2. Heart rate
Group I: 0.125% bupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. Group II: 0.125% levobupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. $p > 0.05$

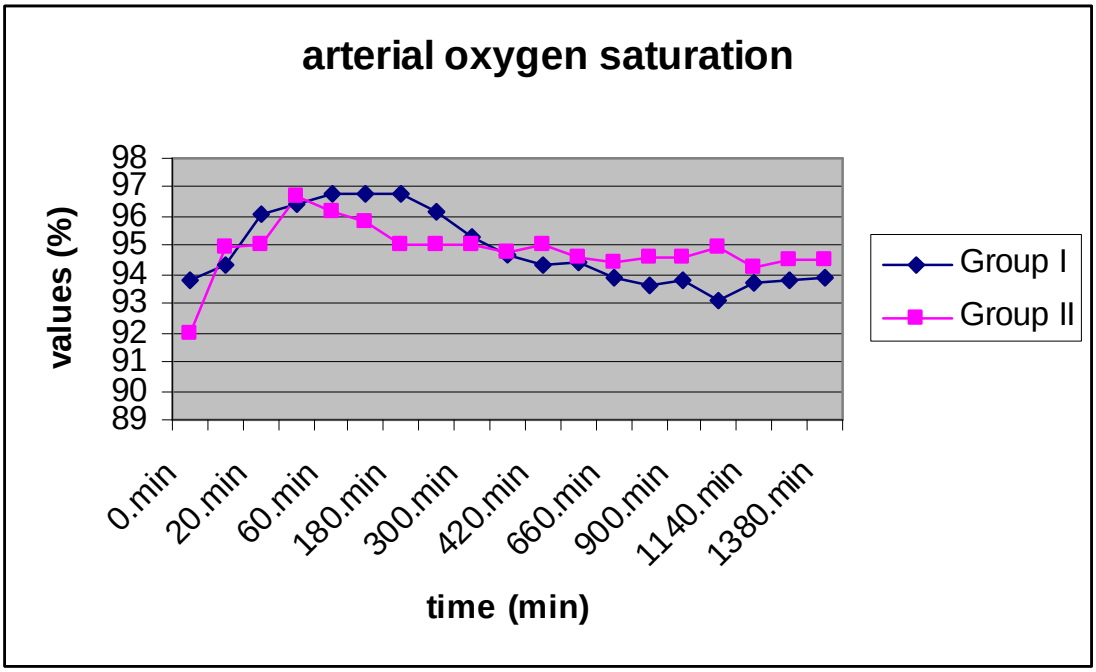

Figure 3. Pulse oxygen saturation

Group I: 0.125% bupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. Group II: 0.125% levobupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. $p > 0.05$

occurred. Our postoperative repeated visits for sedation and respiratory rate monitorization was a precaution for early detection of respiratory depression and provides increased patient satisfaction. None of the patients had a respiratory rate less than 12.

Discussion

The present study demonstrates that levobupivacaine, the pure S(_)-enantiomer of racemic bupivacaine, is as effective as bupivacaine in epidural analgesia when used with fentanyl for major abdominal surgeries. Racemic bupivacaine has been compared to levobupivacaine for epidural, spinal or infiltration anesthesia and for supraclavicular brachial plexus block. The comparisons of these two local anesthetics were planned for lower abdominal surgeries, lower limb surgeries or gynecologic surgeries.[13,17] No

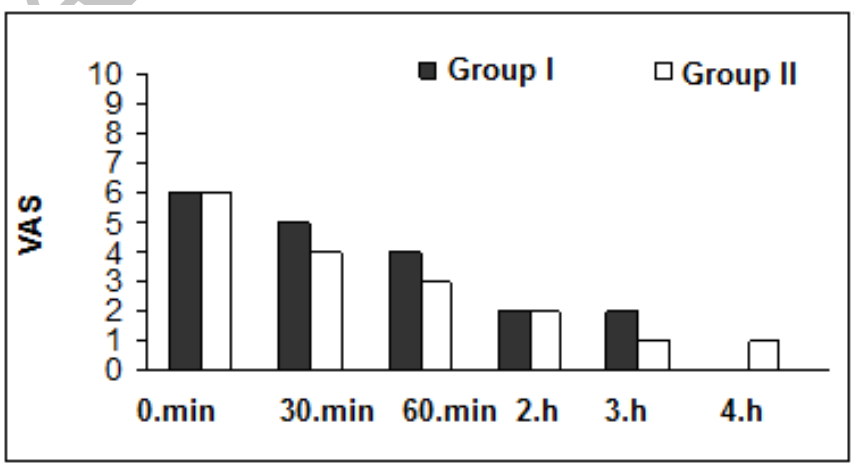

Figure 4. VAS scores

Group I: 0.125% bupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. Group II: 0.125% levobupivacaine and 3 µ/ml fentanyl PCA was used in major abdominal surgery. $p > 0.05$

significant difference for the quality of analgesia was recorded between these local agents and all of them provided efficient clinical anesthesia.[18,19] Morphine or fentanyl was used in order to rise the quality of analgesia in the postoperative period. However there are no comparative studies of efficacy for patient controlled epidural analgesia with fentanyl addition in both lower and upper abdominal surgeries.

In a separate study, three of seven animals given racemic bupivacaine died from sudden onset ventricular fibrillation, whereas the same doses of levobupivacaine produced only nonfatal arrhythmias such as single premature ventricular contractions, bigeminy or couplets. These findings spontaneously reverted to sinus rhythm.[12] We found SVA incidence significantly higher in our setting. Same concentrations of epidural bupivacaine and levobupivacaine with fentanyl increased the incidence of supraventricular arrhythmias but the increase in bupivacaine group was significantly higher than levobupivacaine group. The number of patients with SVA for bupivacaine group in the preoperative period was only 4 but it was recorded in 20 patients after epidural analgesia application. When we checked the results of levobupivacaine group, SVA incidence before local anesthetic application was again 4 but it has reached only up to 9 in the postoperative period. There was not significant variability in the frequencies of VA levels both in preoperative and postoperative periods. The basic cardiac rythm status of the patients was determined first by holter machine before the operation. Then we compared the arrhythmogenic, analgesic and hemodynamic effects of bupivacaine and levobupivacaine in the postoperative period.

Bupivacaine produces local anesthesia by blocking sodium channels and this action is probably the main mechanism responsible for its cardiotoxicity.[18] Because levobupivacaine has less potention for sodium channel blockade and produces less arrhythmias, it has been a popular local anesthetic agent.[20, 21] It was thought that it can be used instead of bupivacaine because of its less toxic side effects to cardiovascular and central nervous system.[22, 23] Corrected QT is used to evaluate the arythmogenic potential of drugs. Levobupivacaine has also a poor influence on QRS or corrected QT.[24]

Previously, ropivacaine was also compared with bupivacaine. The epidural injection of a 1.0% concentration of ropivacaine produced similar sensory and motor block to 0.75% racemic bupivacaine in a similar group of gynecological surgery patients.[25] Casati et al. compared same volume of 0.5% levobupivacaine, bupivacaine and ropivacaine for major orthopedic surgery.[14] They reported that onset, duration and quality of epidural anesthesia were similar. All of the agents provided adequate pain relief via epidural PCA. However, motor block level after levobupivacaine was deeper than the others. In the current trial, levobupivacaine and bupivacaine both showed sufficient sensory/motor separation. We also confirmed that levobupivacaine and bupivacaine have a similar rate of adverse events.

We could not obtain any decrease in periferic oxygenation. This result was similar with the study of Glaser et al.[13] The increase in heart rate between postoperative first and third hours was higher in Group I. This result also supported that bupivacaine has more negative effects on haemodynamic parameters. However this doesn't prop up the results of the trial from Burke et al.[26] These physicians performed spinal anesthesia and they observed additional bradicardy. This diversity may be also related to sympathetic or high sensorial blockade effect of spinal anesthesia.

In an experimental trial, levobupivacaine and bupivacaine were infused intracoronary in order to investigate the direct effects of them. Mean arterial pressure and heart rate of sheeps were increased according to the doses. This result was releated with the stimulation of sympathetic nervous system.[27] The VAS scores did not differ between groups. Several studies

had the same result as our trial.[28, 29] Number of demand or bolus doses of PCA were also similar between groups.

One limitation of our study is that we only assessed the local anesthetic toxicity according to the records of arrhythmogenic and hemodynamic side effects instead of studying the variability of blood levels of local anesthetics.

To summarize, the results of this study indicated that levobupivacaine-fentanyl and racemic bupivacaine-fentanyl show equally effective potencies for epidural analgesia. We aimed to obtain the effects of both solutions on systolic, diastolic arterial blood pressure, periferic oxygen saturation and analgesia. The rate of SVA for bupivacaine group in the postoperative period was statistically higher. The rate of other type of arrhythmias like VA, did not vary. As a result, we concluded that same concentration of epidural levobupivacaine with fentanyl has less arrhythmogenic but similar analgesic potential than bupivacaine in major abdominal surgeries. With regard to the safety of the S-isomer of bupivacaine, further clinical or experimental trials can be planned for different type of surgeries.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

AU carried out the design of the study, developed and wrote the protocol, did the statistical analysis and participated in manuscript preparation. KTS provided assistance in the design of the study and participated in manuscript preparation and did the statistical analysis. AS provided assistance in the design of study, collected data and participated in manuscript preparation. OE provided assistance in the design of the study and participated in manuscript preparation. All authors have read and approved the content of the manuscript.

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