The Comparison of the Effects of Epidural Bupivacaine and Levobupivacaine on the Autonomic Nervous System and Cardiac Arrhythmia Parameters in Inguinal Hernia Surgeries

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Objective: The aim of this study is to investigate the effects of bupivacaine and levobupivacaine, used to create epidural anaesthesia in inguinal hernia operations, on heart rate variability and cardiac arrhythmia parameters.

Methods: Sixty male patients of the American Society of Anesthesiology (ASA) I-II group, scheduled to be operated on for inguinal hernia surgery with epidural anaesthesia, were randomly divided into two groups. The patients, with a 12-channel Holter recorder (Rozinn RZ153+12 -USA) attached 1 hour before the operation to record until the end of the surgery, were taken into the preparation room and anaesthetised. In group L (n=30), 17 mL of 0.5% levobupivacaine (Chirocain 0.5%-Abbot, El-verum, Norway) was given into the epidural space within 10 minutes, versus 17 mL of 0.5% bupivacaine in (Marcain 0.5%, Astra Zeneca, İstanbul, Turkey) group B (n=30). After 30 minutes, when there was enough block, the operation had been started. Holter recordings, starting 1 hour before the anaesthetic procedure and completed by the end of the operations, were transferred to the computer. The records were evaluated by the cardiologists.

Results: When analysing the frequency effect measurement results of the heart rate variability, it was seen that neither of the medications created any statistically significant change in or among the groups in total, very-low-frequency (VLF), low-frequency (LF), high-frequency (HF) and LF/HF ratio levels. Only normalised low-frequency band was significantly lower in Group L (p=0.013).

Conclusion: In the volumes and concentrations that were used in our study, levobupivacaine and bupivacaine created sensory blockade at the same level on average and did not reduce heart rate variability at the levels of these blockages.

Keywords: Anaesthesia, epidural, levobupivacaine, bupivacaine, arrhythmia

Introduction

Epidural anaesthesia and analgesia techniques are among the most frequently preferred anaesthetic techniques used in surgery and obstetric anaesthesia and also in acute and chronic pain control. The advantages of epidural anaesthesia include less hypotension, titratable local anaesthetics and better haemodynamic stability in patients with heart diseases or with a high risk (1). The main action of an epidural block on the cardiovascular system occurs through the blockage of sympathetic nerve fibres. The changes caused by an epidural block primarily depend on the width of the sympathetic blockage. They can also be affected by some factors such as the direct effects of a local anaesthetic agent on the circulatory centre in the myocardium and brain stem, effects of epinephrine added to the local anaesthetic agent and the blockage of afferent fibres reducing cardiovascular reflexes. Bupivacaine is an amide-derived local anaesthetic that is preferred because of its long-term effect. However, its potential cardiotoxic effect restricts its usage. It can cause malignant arrhythmia, conduction disturbances and myocardial depression. Levobupivacaine is the S(-) enantiomer of bupivacaine and has recently been used in our country. In many studies, it has been suggested that the side effects of levobupivacaine on the cardiovascular and central nervous system are fewer than those of bupivacaine and that the time of onset and duration of action are similar in both agents (2, 3). The opinion that it can be an alternative agent for patients with comorbid heart disease has gained importance.

The regulation of heart rate is a result of mutual dynamic interactions between the sympathetic and parasympathetic systems. Efferent sympathetic and vagal activities related to the sinoatrial (SA) node are simultaneous in each cardiac cycle. Because

of continuous change in the sympathetic–parasympathetic balance, fluctuations occur in the sinus rhythm around the mean heart rate. Even if cardiac output is balanced, these two components create tonic effects on the heart. The dominant component is determined with a person's physical and psychological state, and it can be associated with many physiological control processes. Heart rate variability (HRV), which provides information about the sympathetic–parasympathetic balance, is used to measure the cardiac autonomic tone and as an indicator of the cardiorespiratory system. Decreased HRV is related to increased sympathetic and decreased vagal modulation. However, these autonomic changes coexist with elevated malignant ventricular arrhythmia.

In this study, it was aimed to investigate the effects of bupivacaine and levobupivacaine, which are used for creating epidural anaesthesia in inguinal hernia surgeries, on the parameters of HRV and cardiac arrhythmia.

Methods

This study was conducted after receiving ethics committee approval from the Ethics Committee of the Department of Anaesthesiology and Reanimation at Ankara Training and Research Hospital of the Ministry of Health and also after obtaining written informed consents from sixty 18–65-year-old male patients who planned to undergo inguinal hernia surgery and who were in the American Society of Anaesthesiology (ASA) I-II group according to their physical states. The patients who were shorter than 145 cm and heavier than 100 kg, who had contraindications for regional anaesthesia, who were allergic to amide-type local anaesthetics, who had neurological or psychiatric disorders, who had arrhythmia after electrocardiography (ECG) or had a history of a previous arrhythmia treatment, who had electrolyte imbalance and who used drugs that could affect HRV were excluded from the study.

The preoperative evaluations of the patients were conducted the day before the surgery. The patients were informed about the anaesthetic technique and the monitoring procedure in detail, and their written informed consent was received. On the operation day, the patients were taken to the preparation room without the administration of any premedication and were attached to 12-channel Holter device (Rozinn RZ153+12 -USA), which was planned to be attached until the end of the intervention, 1 h before the procedure. They also underwent ECG, oxygen saturation and non-invasive blood pressure monitoring. Peroperative ECG monitoring was performed in DII derivation. Vascular access was established on the dorsal aspect of the left hand with 20G cannula, and Ringer solution including lactate was given until it reached 7 mL kg⁻¹ in 20 min.

After completing the necessary preparation and cleaning the surgical site, epidural anaesthesia was administered from L₃₋₄ or L₄₋₅ interspinous space in the sitting position using an 18

G epidural needle (Braun, Germany) with loss of resistance technique with serum physiologic solution. A 20 G epidural catheter was inserted 3–4 cm into the epidural space. The patients were given the epidural anaesthesia in the lying position. They were randomly divided into the following two groups: Group L (levobupivacaine group) and Group B (bupivacaine group). The study drug was used as a 3 mL test dose, and the epidural catheter was not placed in the intrathecal space or intravascularly after waiting for 5 min. The patients were given oxygen at a rate of 3 L min⁻¹.

Levobupivacaine (Chirocain 0.5%, Abbott, El-verum, Norway) of 17 mL 0.5% in Group L (n=30) and bupivacaine (Marcaine 0.5%, Astra Zeneca İlaç Sanayi ve Tic. Ltd. Şti, İstanbul, Turkey) of 17 mL 0.5% in Group B (n=30) were administered into the epidural space within 10 min. The end time of the injection was accepted to be 0 min for the evaluations. Sensory blockade was assessed using a 22 G needle tip. Evaluations were conducted with 5 min intervals for the first 30 min and with 10 min intervals for the following time periods. In the patients with an adequate blockade level, the intervention was initiated at the 30th minute. On the other hand, the patients with inadequate blockade were given an additional local anaesthetic and analgesic, and the doses of these agents were recorded. The time of reaching the maximum sensorial level by sensory blockade was also recorded.

Haemodynamic evaluations of the patients were performed using systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures, heart rates and oxygen saturations. These parameters were recorded with 5 min intervals during the intervention and with 30 min intervals after the intervention in addition to the baseline values recorded preoperatively.

The side effects including hypotension, desaturation, bradycardia and nausea-vomiting were recorded. If a decrease of more than 30% from the baseline value was observed in SAP, the patient was evaluated to have hypotension and was treated with a rapid crystalloid solution and/or ephedrine. The amounts of fluid and ephedrine were recorded. When the heart rate was 50 beats per min, the patient was evaluated to have bradycardia and was treated with atropine. The amount of atropine used was also recorded.

The recordings of the Holter device, which began 1 h before the anaesthetic procedures and were completed by the end of the surgery, were transferred to the computer and evaluated through Rozinn for Windows® (H4W+ Version 10.00d) program by a cardiologist. Time and frequency effect parameters of heart rate variability were measured. The recordings were evaluated as pre-anaesthesia period and anaesthesia period, and the mean of each period was calculated separately. Moreover, the recordings of the Holter monitoring were also scanned to check for arrhythmia.

In the evaluation of HRV, standard deviation between all normal two beats (SDNN), root mean square of the succes-

Table 1. Intergroup and within-group comparisons of haemodynamic parameters

	Group B (n=30)			Group L (n=30)			*p
	Before anaesthesia	During anaesthesia	**p	Before anaesthesia	During anaesthesia	**p	
SAP (mmHg)	132.8±14.1	124.0±26.3	0.058	136.6±14.6	126.8±12.7	0.001	0.151
DAP (mmHg)	80.9±9.9	77.4±8.9	0.027	85.1±12.5	77.7±8.5	<0.001	0.143
MAP (mmHg)	96.7±10.8	94.0±12.0	0.112	101±12.7	92.2±11.1	<0.001	0.027
HR (beat min ⁻¹)	73.8±11.7	74.0±11.9	0.681	81.3±13.7	77.8±12.1	0.030	0.050
SpO ₂ (%)	97.3±1.9	97.7±16.7	0.923	98.1±1.2	98.3±1.1	0.956	0.981
*p: p-value of the difference between the bupivacaine and levobupivacaine groups before and during anaesthesia; **p: p-value of the within-group difference before and during anaesthesia; Data are presented as mean±standard deviation. SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; HR: heart rate; SpO ₂ (%): peripheral oxygen saturation							

sive differences (RMSSD) and the number of neighbouring two normal beat intervals with more than 50 ms (pNN50) were used as time measurements. As frequency measurements, change in the intervals between all normal two beats (total), very low-frequency band (VLF), low frequency band (LF), high frequency band (HF), LF/HF ratio, normalised low frequency band (LFnu) and normalised high frequency band (HFnu) were used.

Statistical analysis

Statistical analysis was performed using the SPSS 10,0 software program (IBM SPSS Statistics, Chicago, IL, USA). The numerical variables with normal distribution were presented as mean±standard deviation, and the ones without normal distribution were presented as median (minimum–maximum). On the other hand, categorical variables were reported as percentage. Intergroup comparison of categorical variables and identification of the relationships were performed using Pearson's Chi-square test. Student's t-test and Mann–Whitney U test were employed for comparing the numerical variables showing normal distribution and those not showing normal distribution between the groups, respectively. In within-group evaluations, the paired t-test was used for comparing the variables displaying normal distribution. Wilcoxon test was used for comparing the variables without normal distribution. In all evaluations, p<0,05 was accepted to be significant.

Results

In the intergroup evaluation, no statistically significant difference was observed in terms of age, weight, height, duration of intervention and ASA physical state. Moreover, there was no statistically significant difference with regard to maximal sensorial blockade level. It was observed that maximum blockade levels were reached at the T7 levels on average in both groups.

In terms of SAP, no statistically significant difference was observed between the groups (p=0.151). In the within-group comparison, there was a decrease in SAP in Group B and Group L compared to the pre-anaesthesia period. This decrease, which was not clinically significant, was statistically significant in Group L (p=0.001) (Table 1).

Moreover, a statistically significant difference was not observed in the intergroup comparisons with regard to DAP (p=0.143). In the within-group evaluations, a statistically significant decrease was found in DAP both in Group B (p=0.027) and Group L (p<0.001) compared to the pre-anaesthesia period (Table 1).

The groups were compared also with regard to MAP, and a statistically significant difference was observed (p=0.027). In the within-group evaluations, a decrease in MAP was found in Group B and Group L. This decrease was not clinically significant but was statistically significant in Group L (p=0.001) (Table 1).

With regard to heart rate and peripheral oxygen saturation, no statistically significant difference was found in the intergroup and within-group comparisons (Table 1).

When the effects on arrhythmia parameters were examined with the Holter recordings, no arrhythmia or conduction disorders were encountered in both groups.

In the analysis of time effect measurement results on heart rate variability, it was revealed that both bupivacaine and levobupivacaine decreased the SDNN values and that this decrease was statistically significant in the bupivacaine group (p=0.047) but was statistically insignificant in the levobupivacaine group (p=0.232). Between the two groups, no statistically significant difference was observed in terms of the decrease in the SDNN values (p=0.284).

It was also found that both agents did not cause a statistically significant change in the RMSSD and PNN50 values in both the within-group and intergroup comparisons (Table 2).

In the evaluation of frequency effect measurement results on HRV, it was observed that both agents did not cause a statistically significant change in total, VLF, LF, HF and LF/HF ratios in the within-group and intergroup comparisons. Only LFnu was significantly lower in Group L (p=0.013) (Table 3).

Discussion

Local anaesthetics have potential cardiovascular toxicities because they block the ion channels in neuron membranes and

Table 2. Intergroup and within-group comparisons of the time measurements of heart rate variability

	Group B (n=30)			Group L (n=30)			*p
	Before anaesthesia	During anaesthesia	**p	Before anaesthesia	During anaesthesia	**p	
SDNN (ms)	67.1±34.6	54.8±21.3	0.047	62.0±22.6	57.3±31.5	0.232	0.284
RMSSD (ms)	39.04±24.5	34.7±21.9	0.357	34.4±16.6	36.9±24.7	0.405	0.218
PNN50 (Median)	4.9	4.9	0.303	3.2	3.9	0.492	0.126
(Minimum-Maximum)	(0.57-47.66)	(0.1-34.3)		(0.39-36.5)	(0.1-44.9)		

*p: p-value of the difference between the bupivacaine and levobupivacaine groups before and during anaesthesia; **p: p-value of the within-group difference before and during anaesthesia; Data are presented as mean±standard deviation, median for PNN50 (Min–Max). NN interval: intervals between successive two normal beats from the SA node. SDNN: standard deviation of all NN intervals; RMSSD: root mean square of the successive differences; pNN50: proportion of NN50 number to the total NN interval number

Table 3. Intergroup and within-group comparisons of the frequency measurements of heart rate variability

	Group B (n=30)			Group L (n=30)			*p
	Before anaesthesia	During anaesthesia	**p	Before anaesthesia	During anaesthesia	**p	
Total (ms ²)	2479.4 (867.2–22311.9)	1965.1 (724.0–4627.0)	0.153	2244.5 (754.0–5816.6)	1875.4 (607.5–10565.9)	0.898	0.280
VLF (ms ²)	1857.7 (142.9–15237.9)	1548.5 (696.7–3484.5)	0.142	1522.8 (653.1–4980.8)	1459.0 (14.61–7233.2)	0.911	0.237
LF (ms ²)	418.6 (93.4–6122.0)	356.5 (22.3–1552.6)	0.156	558.3 (58.2–1253.7)	381.7 (16.8–2707.2)	0.779	0.525
HF (ms ²)	112.3 (24.5–951.4)	111.2 (5–699)	0.395	102.7 (15.0–473.6)	109.0 (2.9–767.8)	0.239	0.391
LF/HF ratio	3.6 (1.1–10.4)	2.5 (1.0–8.2)	0.053	3.6 (0.9–26.5)	3.2 (0.9–16.0)	0.189	0.813
LFnu	26.6 (7.9–58.5)	20.2 (3.1–66.8)	0.064	28.7 (6.9–62.8)	22.8 (2.0–60.3)	0.013	0.506
HFnu	7.2 (1.5–20.9)	7.8 (0.4–22.1)	0.453	5.2 (1.3–13.8)	6.7 (0.4–28.6)	0.169	0.988

*p: p-value of the difference between the bupivacaine and levobupivacaine groups before and during anaesthesia; **p: p-value of the within-group difference before and during anaesthesia. Data are presented as mean (minimum value–maximum value). Total Power: change in all NN intervals, VLF: very low frequency band; LF: low frequency; HF: high frequency; LF/HF ratio: LF (ms²)/HF (ms²) ratio; LF nu: normalised LF (LF normalised units); HF nu: normalised HF (HF normalised units)

also the channels in other excitable tissues. The toxicity risk is higher in long-term local anaesthetic agents. Cardiotoxicity probably results from their direct and indirect (suppression of autonomic nervous system) effects on the heart. Their direct effects lead to decreased cardiac output, hypotension, ventricular tachycardia that can cause cardiac arrest and cardiotoxicity including ECG changes showing heart block. Their indirect effects can include the blockage of sympathetic cardiac innervation or other SSS-related mechanisms. The blockade of myocardial Na⁺ channels causes delayed conduction and prolonged QRS. Moreover, the blockade of potassium and Ca⁺⁺ channels can also result in cardiotoxicity.

Casati et al. (4) used 0.5% levobupivacaine, bupivacaine and ropivacaine for the epidural anaesthesia procedures of 45 patients undergoing total hip replacement. They encountered hypotension in 26% of the patients in the levobupivacaine group, in 46% of the patients in the bupivacaine group and in 33% of the patients in the ropivacaine group. Moreover, they reported that bradycardia developed in 20% of the patients in

the levobupivacaine group, in 13% of the patients in the bupivacaine group and in 26% of the patients in the ropivacaine group. They associated these high rates of hypotension and bradycardia development with the selected patient group, low volume of crystalloid infusion performed before the epidural block and administration of intraoperative sedation.

In our study, statistically significant but clinically insignificant decreases in blood pressure were observed especially in the patients given levobupivacaine. No significant difference was found between the two groups. This result was attributed to the patient groups with low risk, crystalloid infusion performed before the epidural block and both agents' creating a blockade at almost the same level.

Denson et al. (5) compared the effects of levobupivacaine and dexbupivacaine (at a dose of 2 mg kg⁻¹) on the cardiovascular system in rats. The pyrexia rate of the cells in the nucleus tractus solitarius (NTS), which is the most important part of the brain related to the heart functions, was measured in the

same rats. It was revealed in that study that levobupivacaine caused mild bradycardia in 25% of the rats and that 85% of the rats in this group survived. However, dexbupivacaine led to severe bradycardia and progressive hypotension, and all rats died in this group. In 25% of the rats given dexbupivacaine, malignant ventricular arrhythmia was observed. While the Wenckebach rhythm (second-degree heart block) was seen in all the rats that were given dexbupivacaine, it appeared in 15% of the rats receiving levobupivacaine. The effect of levobupivacaine on NTS function was found to be significantly lower. In another study conducted by Valenzuela et al. (6), in the hearts of Guinea pigs, the power of levobupivacaine for blocking the Na⁺ channels of the heart was significantly lower than that of bupivacaine and dexbupivacaine.

In a study conducted for evaluating relative cardiotoxic potentials of the intravenous administrations of levobupivacaine and bupivacaine in human beings, the cardiovascular effects of levobupivacaine were compared following intravenous (IV) administration of bupivacaine in 14 healthy male volunteers (7). The drugs were given with randomized, double-blind and 10 mg min⁻¹ dose of infusion using the cross method and leaving an at least one-week interval between the administrations for purification. The mean doses of levobupivacaine and bupivacaine were 56.1 mg and 47.9 mg, respectively, and the maximum mean plasma concentrations equivalent to these values were 2.62 and 2.25 µg mL⁻¹. Although the mean total dose and plasma concentrations of levobupivacaine were higher, it created fewer average changes in cardiac variables than bupivacaine. When the changes in heart beat index, acceleration index and ejection fraction were compared from the beginning till the end of infusion, they were significantly larger in the bupivacaine group than in levobupivacaine group. In both the levobupivacaine (not statistically significant) and bupivacaine groups (statistically significant), insignificant changes occurred in PR and corrected QT intervals after infusion, but the effects of bupivacaine were more apparent.

Salomaki et al. (8) reported that cardiovascular collapse developed in a patient after iv administration of 125 mg of levobupivacaine by accident and that the patient healed without any sequela, which was attributed to the lower effect of levobupivacaine on the K⁺ channels of the heart.

Considering the different effects of levobupivacaine and bupivacaine on the heart revealed by the animal and human studies mentioned above, the use of 0.5% levobupivacaine (100 mg) and 0.5% bupivacaine (100 mg) in epidural anaesthesia were compared with regard to their effects on cardiac arrhythmia, conduction change and HRV. The difference observed between the two drugs in preclinical and experimental studies was not seen in clinical studies. In our study, arrhythmia and conduction disturbances were not encountered in any patient.

HRV can be defined as changes in the sinus rhythm over time. Because the sympathetic-parasympathetic balance con-

tinuously changes, fluctuations occur around the mean heart rate. HRV, which provides information about the sympathetic-parasympathetic balance, is used to measure the cardiac autonomic tone and an indicator of the cardiorespiratory system (9). Decreased HRV increases the risk for arrhythmia (10).

Various studies demonstrated that the space between successive heart beats, namely R-R variability, differs in healthy individuals (11-15). Malliani et al. (16) stated that the LF/HF ratio could be used for measuring the sympathovagal balance.

Fleisher et al. (17) conducted a study with 20 patients who planned to undergo radical retropubic prostatectomy surgery for determining the effects of general and regional anaesthesia on peripheral and cardiac autonomic tone. They divided the patients into the following two groups: the patients administered general anaesthesia and the patients administered epidural anaesthesia. They performed the spectral power analysis of typical R-R intervals. As a result, in the intraoperative period, a significant increase in the LF/HF ratio was observed in the epidural anaesthesia group with the mean sensorial blockade level of T3. This increase was in favour of dominance. While no change was seen in the epidural anaesthesia group in the postoperative period, a statistically significant increase in the sympathetic tonus was found in the general anaesthesia group. They thought that this increase in the LF/HF ratio is associated with decreased HF power. HF is an indication of the parasympathetic system. Because the vagal fibres were not blocked by epidural anaesthesia, this result was explained by the reflex effect. In other words, the parasympathetic system rapidly responds to the baroreceptor stress changing because of decreased blood pressure. The researchers stated that the prevention of normal blood pressure under epidural anaesthesia may have resulted from the withdrawal of the parasympathetic tonus. This withdrawal provides the maintenance of the normal homeostasis mechanism. In conclusion, it was specified that sympathovagal balance in both the general anaesthesia group and epidural anaesthesia group changed in the perioperative period and that this condition may have been associated with an elevated risk of perioperative ischaemia especially in patients with ischaemic heart disease.

Tanaka et al. (18) divided 20 patients into two equal groups and examined the effects of cervical and epidural anaesthesia techniques on HRV and spontaneous baroreflex sensitivity. In the study planned to confirm the accuracy of the hypothesis that 'lumbar epidural anaesthesia can lead to sympathetic dominance, but cervical epidural anaesthesia can increase the HF component of HRV as a result of sympathectomy in the heart', 1.5% plain lidocaine was given from the epidural catheter placed in the cervical C6-7 interval, and the mean C3/T8 sensory level was obtained. As a result, a remarkable decrease was seen in the systolic blood pressure and heart rate, but contrary to expectations, both LF and HF components decreased, and no change occurred in the LF/HF ratio. The

same agent and dose were used in lumbar epidural anaesthesia, and blockade at the T10 level was obtained on average. Ultimately, a decrease in the systolic blood pressure and an increase in the heart rate were observed and an increase in the LF/HF ratio was seen, which was indicative of sympathetic dominance. Although Fleisher et al. (17) obtained higher analgesia levels (T3) in their study, the changes of HRV that occurred with lumbar epidural anaesthesia were consistent with the study reporting an increased LF/HF ratio in patients with spontaneous ventilation after lumbar epidural anaesthesia was given with bupivacaine.

Conclusion

In our study, bupivacaine and levobupivacaine decreased SDNN (which was statistically significant for bupivacaine but statistically insignificant for levobupivacaine), and in other words, decreased HRV. However, no statistically significant difference was observed between the two groups. Moreover, a statistically significant difference was not found between the two agents with regard to other time effect measurements. In frequency effect measurement results, both drugs did not create any statistically significant change in total, VLF, LF, HF and LF/HF ratio values in the within-group and intergroup comparisons. Consequently, levobupivacaine and bupivacaine in the volumes and concentrations used in our study formed a sensory blockade at approximately the same levels, and they do not reduce HRV at these blockage levels.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ministry Health Ankara Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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