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The Effect of Intraspinal Bupivacaine *versus* Levobupivacaine on the QTc Intervals during Caesarean Section: A Randomized, Double-blind, Prospective Study

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Abstract: The aim of this study was to describe whether or not spinal anaesthesia with bupivacaine *versus* levobupivacaine has any effects on the QTc interval during caesarean section. Sixty healthy pregnant women scheduled for elective caesarean section were randomized to spinal anaesthesia with either bupivacaine (the bupivacaine group) or levobupivacaine (the levobupivacaine group). ECG recordings were performed prior to spinal anaesthesia at baseline (T1), 5 min. after spinal anaesthesia, but before uterine incision (T2), and after skin closure (T3). QT intervals were calculated and corrected with the patients' heart rate according to the Bazett formula. Compared with baseline values, mean maximum QTc intervals at T2 and T3 were significantly longer in the levobupivacaine group, but only at T2 in the bupivacaine group. In addition, compared with the bupivacaine group, the QTc maximum interval at T3 was significantly longer in the levobupivacaine group. At T2, the QTc maximum intervals were longer than baseline in both groups. By the end of the surgery, the prolongation of the QTc interval had disappeared in the bupivacaine group but not in the levobupivacaine group.

The QT interval is defined as the measurement of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents the total period of the left ventricle's depolarization and its repolarization. QT prolongation is associated with increased risk of ventricular arrhythmias, leading to polymorphic ventricular tachycardia (Torsades de Pointes) and ventricular fibrillation [1]. The myocardial conduction changes (prolongation of PQ or QT intervals or QRS widening) are assumed to be early signs of drug-related cardiac toxicity and might be determined even in the absence of any significant changing in contractility [2]. Prolongation of the QT interval can be either hereditary or acquired. It is associated with different medications, as well as cardiac, neurological and electrolyte disorders. Several cardiac and non-cardiac medications, including anaesthetics [3], can also interfere with cardiac repolarization and prolong the QT interval, and sometimes may cause drug-induced Torsades de Pointes and even sudden cardiac death [4–7].

Spinal anaesthesia is commonly used in emergency and elective caesarean section because it provides rapid and adequate anaesthesia. Regional anaesthesia techniques eliminate the increased catecholamine levels that result from laryngoscopy and intubation. Increased plasma catecholamine concentrations and sympathetic activity are related with increased incidence of ventricular arrhythmias and even sudden death because of prolonged QT interval [8,9]. In addition, regional techniques eliminate or decrease the need for induction agents, volatile anaesthetics, opioids, muscle relaxants and neuromuscular reversal intra-operatively and postoperatively, all of which have variable effects on QT intervals [5,10,11]. Both bupivacaine and levobupivacaine (both the L-form and the S enantiomer of bupivacaine) are local anaesthetics routinely used in anaesthesia practice [12]. Bupivacaine is more cardiotoxic than levobupivacaine [13]. The toxicity was attributed to its high affinity to the myocardial Na^+ channel [14]. Because of its toxicity, new agents (e.g. levobupivacaine and ropivacaine) were developed to obtain secure anaesthesia procedure [15]. Previous case reports indicated that spinal anaesthesia with both bupivacaine [16–18] and levobupivacaine [19] has been used successfully in patients with long QT syndromes. Some studies in males have evaluated QTc following intraspinal bupivacaine [20] and cardiac effects of intravenous dosing of bupivacaine and levobupivacaine [12].

The aim of this study was to describe whether or not bupivacaine *versus* levobupivacaine for spinal anaesthesia has any effect on QT interval during caesarean section.

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Materials and Methods

Ethics. Ethical approval for this study was provided by the Ethical Committee of Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Individuals. After giving written informed consent, 60 healthy pregnant women scheduled for elective caesarean section were randomly selected by computer-based software to receive either bupivacaine or levobupivacaine for spinal anaesthesia. Patients were excluded if obese (body mass index > 30 kg/m^2), less than 155 cm tall, less than 18 years or older than 40 years or had a systolic arterial pressure of less than 100 mmHg. We also excluded patients who had diabetes mellitus (gestational or chronic), hypertension (gestational or chronic), chronic obstructive pulmonary disease, baby in breech position, known foetal abnormalities, contraindications to spinal anaesthesia, congenital or acquired QTc interval prolongation (QTc ≥ 440 ms), family history of long QT syndrome, serum electrolyte (potassium, magnesium and calcium) abnormalities and patients taking medications that had any effect on the QTc interval (e.g. tricyclic antidepressants, antiarrhythmics, b-adrenergic antagonists or calcium channel blockers), or those having any cardiac rhythm other than sinus rhythm on preoperative ECG. Patients were also excluded from the study in case of sympathetic stimulation, such as retching, vomiting or agitation.

Study design. All data were collected from 8:00 a.m. to 12:00 p.m. to minimize the effects of day–night changes on the QTc interval. To assure blinding, test solutions were prepared by a consultant anaesthesiologist. Noninvasive blood pressure, 3 and 12 lead electrocardiograms and peripheral oxygen saturation were monitored (GE Healthcare, D-FPD15-00, Helsinki, Finland) and recorded as baseline data. After venipuncture, both groups received a rapid infusion of lactated Ringer's solution for 10–15 min. (10 mL/kg warmed to body temperature just before spinal anaesthesia). After delivery, all patients were intravenously given 30 international units (IU) of oxytocin (10 IU bolus dose over 10 sec. and 20 IU infusion in lactated Ringer's solution of 1000 ml over 30 min. This protocol of oxytocin is routinely used in our hospital).

Spinal anaesthesia. A consultant anaesthesiologist prepared 12 mg of 0.5% hyperbaric bupivacaine for the bupivacaine group or 0.5% levobupivacaine for the levobupivacaine group. After each patient was placed in the sitting position, lidocaine was used for skin anaesthesia at either L3-4 or L4-5 vertebral interspace. A 27-gauge pencil-point needle via a 22-gauge introducer was inserted, and intraspinal injection was performed over ten seconds. The patients were placed in supine with left tilt position until delivery and evaluated with blinded needle by the pinprick test at 3rd, 5th, 7th and 10th min and then at 5-min. intervals. No patient needed to extra anaesthetic intervention or supplementation.

The patients' blood pressure and heart rate were recorded at 3, 5, 7 and 10 min. and then at 5-min. intervals. Hypotension (defined as a decrease in systolic blood pressure below than 90 mmHg) was treated by using intravenous boluses of ephedrine 10 mg. We divided ephedrine usage into four groups: none, one dose is defined as mild hypotension, two and three doses are defined as moderate hypotension and four doses are defined as severe hypotension.

Measurement of QTc intervals. Twelve leads of ECG recordings were performed before spinal anaesthesia at baseline (T1), 5 min. after spinal anaesthesia and before uterine incision (T2), and after skin closure (T3).

To exclude individual variability, two cardiologists (blinded as to the drug received by the volunteers) assessed QTc measurements separately on 12 leads of the standard ECG. We computed heart rate from the three R-to-R intervals prior to the measured QTc intervals from the beginning of the QRS complex to the end of the T wave. All QT intervals in milliseconds were corrected with the patient's heart rate according to the Bazett formula ($QTc = QT/\sqrt{RR}$). Each measurement was a mean of three consecutive QTc intervals. T waves with low amplitude (<0.1 mV) were excluded. In this study, QTc dispersion (QTc_{Disp}) is defined as the difference between the maximum and minimum QTc intervals measured from the entire 12-lead standard ECG for each point.

Statistical analysis. We determined that 23 patients were needed for each group based on an alpha level of 0.05 and power set at 0.9, to discover a mean difference of 30 ms with a standard deviation of 30 ms for the QTc interval between two groups [20]. We performed statistical analysis using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). For post hoc comparisons of repeated measurements, a paired-sample *t* test was used for within group contrasts with the Bonferroni correction, after testing the overall effect using repeated measures analysis of variance analysis. The independent-sample *t* test was used between groups. Nonparametric data were evaluated with the x^2-test. $p < 0.05$ was considered as significant for between groups. $p < 0.016$ (QTc) and $p < 0.005$ (hemodynamic analysis) were considered as significant for within group after Bonferroni correction.

Results

For this study, the 60 participating patients were randomized. Fig. 1 shows reasons for exclusion. From the levobupivacaine group, these include ECG recording failure (1) and spinal anaesthesia failure (1), and in the bupivacaine group, ECG recording failure (2) and agitation (1 patient who had to be sedated). There was no statistically significant difference between groups regarding age, weight, height, maximum sensory block, duration of surgery, the number of patients who needed ephedrine and total ephedrine usage (table 1). Likewise, there was no difference between the groups regarding frequency and severity of hypotension according to total ephedrine usage (table 2) and ephedrine usage before the second ECG recording (table 1).

Heart rates and mean arterial pressure in both groups were similar at baseline; however, in the levobupivacaine group, heart rate after 3 min. of spinal anaesthesia was statistically higher than baseline. In the bupivacaine group, heart rate showed no difference compared with baseline. Mean arterial pressures were lower in both groups (fig. 2).

Mean maximum QTc (QTc_{Max}) intervals at T2 and T3 were significantly longer in the levobupivacaine group, as compared to baseline ($p < 0.016$).The mean minimum QTc (QTc_{Min}) interval at T3 in the levobupivacaine group was significantly longer as compared to baseline. In the bupivacaine group, only the QTc_{Max} interval was longer at T2 as compared to baseline ($p < 0.016$). Compared with the bupivacaine group, the QTc_{Max} interval at T3 was significantly longer in the levobupivacaine group ($p < 0.016$). Dispersions of QTc intervals were similar in both groups at T1, T2 and T3 (table 3).

Discussion

This study evaluated the effect of bupivacaine and levobupivacaine for spinal anaesthesia on QT interval during caesarean section. Neither is currently acknowledged as a drug which can affect the QT interval [11].

The normal acceptable range of the QTc interval is 380–440 millisecond healthy individuals depending on age and

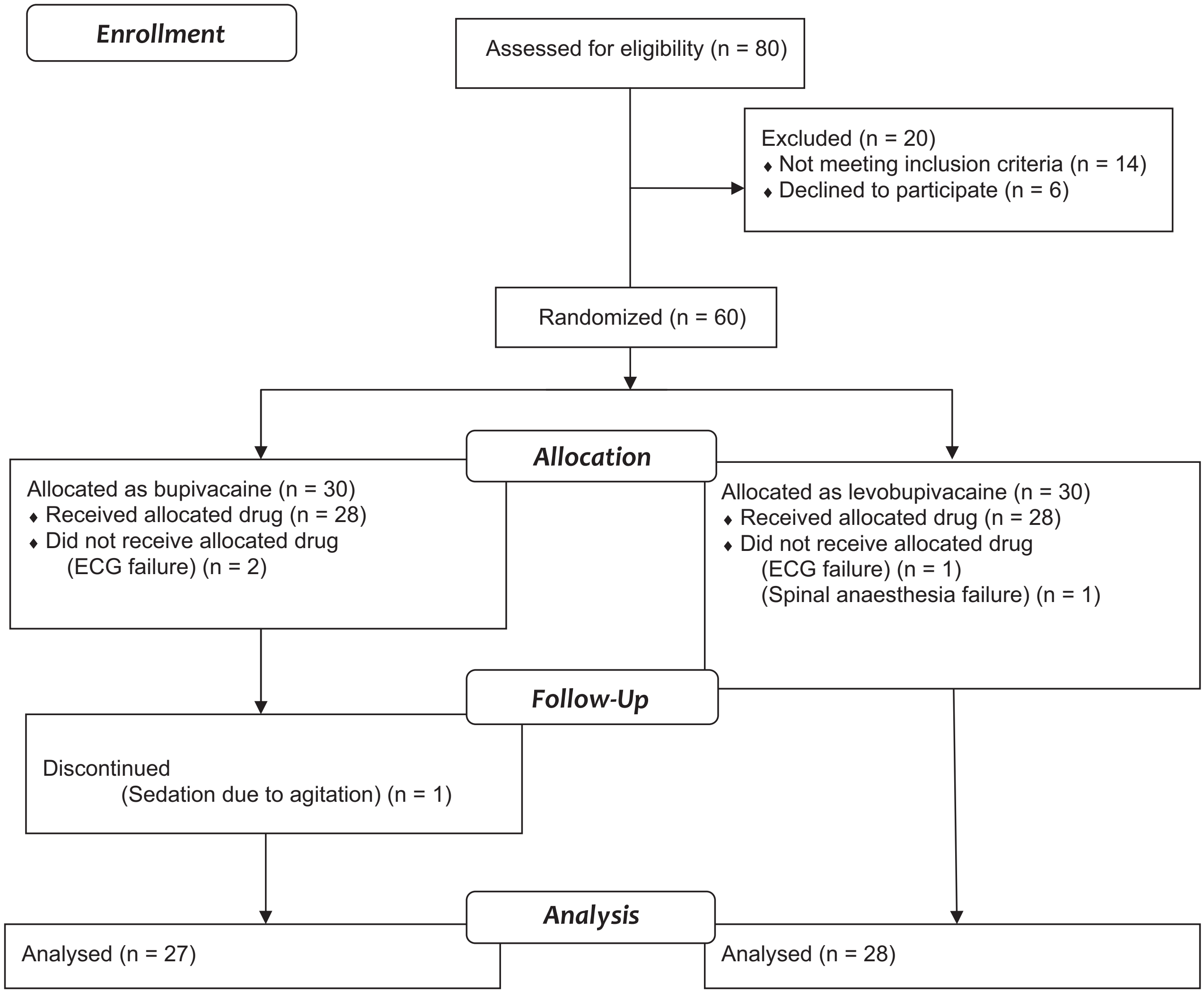

Fig. 1. Flow diagram of the study.

Table 1.
Patient characteristics, undergoing caesarean section under spinal anaesthesia, randomized to bupivacaine (bupivacaine group) or levobupivacaine (levobupivacaine group).

	Bupivacaine group (n = 27)	Levobupivacaine group (n = 28)
Age (year) [Mean ± S.D. (range)]	29.1 ± 3.6 (23–40)	30.4 ± 3.5 (19–39)
Height (cm) [Mean ± S.D. (range)]	158.0 ± 7.3 (155–166)	157.7 ± 4.7 (155–167)
Weight (kg) [Mean ± S.D. (range)]	75.3 ± 14.2 (55–102)	77.92 ± 11.3 (58–97)
Gestational week at delivery (weeks) [Mean ± S.D. (range)]	40.0 ± 0.9 (38–41)	40.1 ± 1.0 (38–41)
Maximum sensory block (median, range)	T4 (T6–T2)	T4 (T6–T2)
Duration of surgery (min) [Mean ± S.D. (range)]	38.7 ± 6.7 (25–50)	37.9 ± 6.7 (30–55)
Ephedrine dose after spinal anaesthesia to second ECG recording (mg) [Mean ± S.D. (range)]	9.8 ± 9.2 (0–30)	8.6 ± 9.2 (0–30)
Number of patients used ephedrine (n) (%)	20/27 (74%)	18/28 (64%)
Total cumulative ephedrine per patient (mg) [Mean ± S.D. (range)]	15.4 ± 12.9 (0–40)	13.2 ± 13.0 (0–40)

ECG = Electrocardiogram, T4 = Blockage of fourth thoracic vertebral nerve.

gender [21,22]. Although many formulas, including Bazett, Fridericia, Framingham and Sarma, are used to calculate QTc interval, the best formula has not yet been determined. No formula provides any particular advantage over the simple Bazett formula [23], the most preferred method to correct QT intervals. To exclude possible variation due to the heart rate, the QTc_{Min} and the QTc_{max} were calculated based on ECG readings in this study. After these, the QTc_{Disp} was calculated by

Table 2.
Severity of hypotension according to ephedrine usage in patients undergoing caesarean section under spinal anaesthesia randomized to bupivacaine (bupivacaine group) or levobupivacaine (levobupivacaine group).

	Bupivacaine group (n = 27)		Levobupivacaine group (n = 28)	
	T2	T3	T2	T3
None (n)	9	7	11	10
Mild hypotension – once (n)	11	7	11	4
Moderate hypotension – two or three times (n)	7	11	6	13
Severe hypotension – four times (n)	0	2	0	1

T2, 5 min. after spinal anaesthesia and before uterine incision, T3, after skin closure.

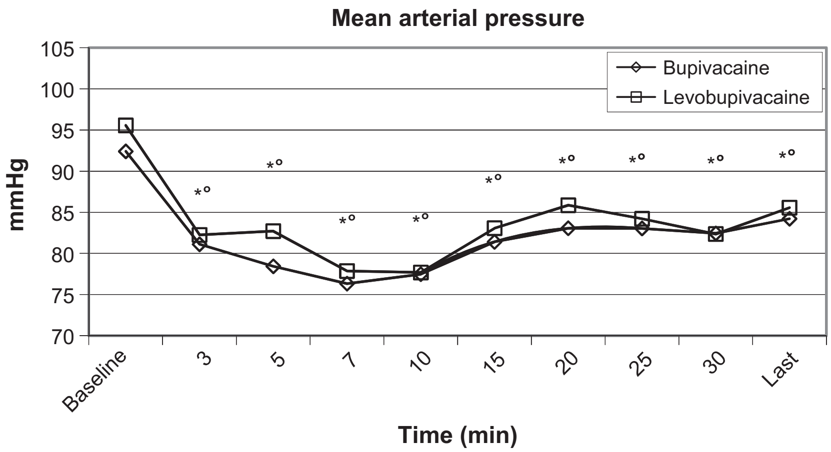

Fig. 2. Mean arterial pressure in patients undergoing caesarean section under spinal anaesthesia randomized to bupivacaine group or levobupivacaine group. °$p < 0.05$ when compared to baseline in the bupivacaine group. *$p < 0.005$ when compared to baseline in the levobupivacaine group.

subtracting the QTc_{Max} and the QTc_{Min}. FDA published a guide for clinical evaluation of QT/QTc prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs [24].

In both groups, QTc_{Max} intervals at T2 were statistically different when compared to baseline separately. There was no difference between groups as to QTc_{Max} at T2. Although it is known that levobupivacaine has fewer and less cardiovascular effects than bupivacaine, QTc_{Max} interval at T3 was statistically different in the levobupivacaine group compared with both the baseline and bupivacaine groups. A previous study [12] showed a slight increase in the QTc interval in the bupivacaine group, but that study compared IV bupivacaine to IV levobupivacaine in male volunteers and found no difference in QT intervals. However, our population was both women [25] and pregnant women, and our route was intraspinal. Moreover, QTc prolongation during spinal anaesthesia with bupivacaine was confirmed in male patients during spinal anaesthesia [20], but in that study, measurement was only at the 15th min.; no information was reported after that time. In our study, T3 was coincided with approximately the 37th and the 38th min. after spinal anaesthesia. These prolongations at T2 might be compatible with the effect of lumbar sympathetic blockage of spinal anaesthesia. As sympathetic stimulation is a provoker event for both prolongation of the QTc interval and episodes of TdP in patients without prolonged QT [20], it is supposed that lumbar sympathetic block has the protective effect for prolongation of the QTc interval. On the other hand, lumbar sympathetic block could have caused rapid distributive effect and then thoracic sympathetic nerves including the fibres supplying the heart (T1–4) stimulated as compensatory reaction to hypotension. However, in our groups, median of the sensorial block level was at T4 (T2–T6).

As motor block is less prevalent with levobupivacaine [26], the L-form of bupivacaine could have been less efficient on these fibres. Compared with levobupivacaine, control of the central nervous system on the heart might have been more affected by bupivacaine due to its higher potency. Thus, cardiac control could have provided by peripheral nerve system. This could explain the differences in the levobupivacaine group in both QTc_{Min} and QTc_{Max}.

The toxic effect of local anaesthetics on myocardial contractility and cardiac conduction is attributed to alteration of Ca^{++} handling [15]. Systemic absorption of these agents is limited during spinal anaesthesia. In those standard doses, intraspinal injections are not expected to cause QTc prolongation, even intravenously; thus, systemic absorption cannot be a reason for this prolongation in the levobupivacaine group.

A prolonged QTc interval after oxytocin injection during caesarean section has been reported [27]. To exclude this effect, ECG at T2 was recorded at 5 min. after supine posi-

Table 3.
Evaluation of QTc intervals according to the Bazett correction in patients undergoing caesarean section under spinal anaesthesia randomized to bupivacaine (bupivacaine group) or levobupivacaine (levobupivacaine group).

	Bupivacaine group (n = 27)	Levobupivacaine group (n = 28)	*p*-values (between groups)	*p*-values (compared to baseline)	
				Bupivacaine group (n = 27)	Levobupivacaine group (n = 28)
QTc_{Min} at T1 [Mean ± S.D. (range)]	380.3 ± 21 (323–427)	385.1 ± 24 (333–428)	0.4	–	–
QTc_{Min} at T2 [Mean ± S.D. (range)]	382.4 ± 23 (329–423)	395.3 ± 27 (353–442)*	0.06	0.6	0.02
QTc_{Min} at T3 [Mean ± S.D. (range)]	389.2 ± 20 (361–424)	400.8±20 (367-435)$^{\#*}$	0.03	0.1	0.000
QTc_{Max} at T1 [Mean ± S.D. (range)]	418.3 ± 23 (378–440)	423.9 ± 26 (379–440)	0.4	–	–
QTc_{Max} at T2 [Mean ± S.D. (range)]	428.0 ± 19 (374–460)†	437.4 ± 28 (390–481)*	0.1	0.007	0.005
QTc_{Max} at T3 [Mean ± S.D. (range)]	426.1 ± 19 (378–447)	440.4 ± 20 (408–485)$^{\#*}$	0.009	0.07	0.000
QTc_{Disp} at T1 [Mean ± S.D. (range)]	38.0 ± 23 (0–69)	38.8 ± 15 (16–82)	0.9	–	–
QTc_{Disp} at T2 [Mean ± S.D. (range)]	45.6 ± 24 (4–96)	42.1 ± 19 (10–79)	0.6	0.1	0.4
QTc_{Disp} at T3 [Mean ± S.D. (range)]	37.0 ± 19 (4–86)	39.7 ± 13 (15–65)	0.5	0.8	0.8

#$p < 0.05$ between groups.
†$p < 0.016$ when compared to baseline in the bupivacaine group after Bonferroni correction.
*$p < 0.016$ when compared to baseline in the levobupivacaine group after Bonferroni correction.
QTc_{Min}, minimum QTc interval, QTc_{Max}, maximum QTc interval, QTc_{Disp}, dispersion of QTc intervals. T1, prior to spinal anaesthesia at baseline, T2, 5 min. after spinal anaesthesia and before uterine incision and T3, after skin closure.

tion, (providing that was) before uterine incision. All patients were administered a standard oxytocin injection as detailed in the Material and Methods section. Ephedrine also affects QTc [11]. In both groups of our study, ephedrine doses were similar at T2 and T3.

Lower arterial pressure because of spinal anaesthesia does not explain the difference. Although lower arterial tension yields lower uterine perfusion leading to a shorter QTc interval [28], QT prolongation was determined in our study.

Actually, changes on QTc could be affected by many things during spinal anaesthesia. Shortened QTc is supposed because of sympathetic blockage, like in stellate ganglion blockage [29] or thoracic sympathectomy [30], but prolonged QT was showed [20]. Prolonged QTc is supposed by ephedrine used for hypotension [11]. Both laryngoscopy and intubation cause the sympathetic stimulation [31], and prolongation is supposed. In addition, women normally have longer QTc intervals than men [20]. This means that changes in QTc interval are more complex than both expected and known.

QTc_{Disp} may provide an indirect measure of the heterogeneity of myocardial repolarization, which is believed to be both important and useful in the assessment of arrhythmia risk [32,33]. In our study, QTc_{Disp} values did not differ between groups and their baseline values. As QTc_{Min} and QTc_{Max} values were prolonged proportionally while QTc_{Disp} values remained steady. This was also the case in some Class III anti-arrhythmic agents [32,33]. Although it is generally agreed that QTc_{Disp} increases in the LQTS, a correlation between QTc_{Disp} and symptomatic status was not determined [34]. Still, ineffective beta blockade treatment in patients with the LQTS is associated with high level of QTc_{Disp}, which efficiently predicts the efficacy of anti-adrenergic therapy [35]. In addition, cardiovascular mortality and morbidity are affected by prolongation of the QTc interval and QTc_{Disp} independently [36].

Patients with long QT were excluded from the study. Clinically, response to intraspinal injection of local anaesthetics may be different in these patients, and prolongation due to spinal anaesthesia may cause dramatic consequences. It is important to note that although drug-induced QT prolongation is a sensitive indicator of a risk of drug-induced torsades de pointes, prolongation of the QT interval alone does not cause pro-arrhythmia [37].

This study has a several limitations. There were only three ECG recordings intraoperatively and postoperatively. Postoperative ECG recordings could have indicated the length of the prolongation in the levobupivacaine group. Holter monitoring [38] could have provided information about heart rate variability.

In conclusion, at the first period of spinal anaesthesia (before delivery), QTc intervals were prolonged in both groups. The prolongation restored in the bupivacaine group until operation ended, but not in the levobupivacaine group.

Disclosure of Interests

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the study.

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