Effects on QTc Interval of 2 Different Doses of Spinal Anesthesia in Inguinal Hernia Operations

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Background: Cardiac arrhythmia is a significant cause of morbidity and mortality. In this study, through examination of the effects on the QTc interval of different doses of hyperbaric bupivacaine, we investigated the relationship with arrhythmia.

Material/Methods: A total of 60 patients were separated into 2 groups: spinal block was applied with 10 mg bupivacaine to Group S1 and with 15 mg to Group S2. The mean arterial pressure (MAP) and heart rate (HR) values were recorded before the spinal block and at 5 and 30 min after the block and at 60 min postoperatively. By recording the time of the spinal sensory block to reach T10 dermatome (Anaesth T) and the duration of the surgical procedure (Surg T.), the QTc intervals were calculated.

Results: The demographic data were similar in both groups. A statistically significant difference was determined between the S1 and S2 groups between the baseline and the 30 mins after spinal block QTc intervals (p=0.001). No statistically significant difference in HR values was determined between the groups at baseline, 5 min after spinal block, and 1 h after surgery (all p>0.05), but at 30 min after spinal block value there was a statistically significant difference (p=0.010). No statistically significant difference was determined in MAP values between the groups at baseline and 1 h after surgery (p>0.05).

Conclusions: The QTc interval lengthened in a dose-dependent manner after spinal anesthesia was applied with different doses of bupivacaine, but the doses used did not cause any severe arrhythmia.

MeSH Keywords: Anesthesia, Spinal • Arrhythmias, Cardiac • Bupivacaine • Long QT Syndrome

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Background

Cardiac arrhythmia is a frequently encountered problem in the application of anesthesia, and is a significant cause of morbidity and mortality [1,2]. Changes created in the autonomic nervous system and catecholamine discharge may cause arrhythmia, especially during induction and intubation in the application of general anesthesia [3,4]. Heart rhythm disorders can be caused by the sympathetic blockage created during the procedure and the direct cardiotoxic effects of the local anaesthetics in regional anesthesia, which may lead to cardiac arrest [5]. Bupivacaine, which is often used in neuroaxial blockades, is a local anaesthetic known to often cause signalling defect with blockage of the sodium channel, a negative inotropic effect, and arrhythmias [6,7]. Bupivacaine may cause lengthening of the QT distance, together with lengthening of the P-R distance and atrioventricular block, widening in the QRS complex, and ventricular arrhythmia on ECG [8,9].

The QT interval is defined as the gap starting from the QRS complex to the end of the T wave on ECG, which shows depolarization and repolarization of the ventricles [10]. The relationship of the lengthening of the QT interval with ventricular arrhythmia is of primary importance. A study in the USA of an extensive series reported that this interval was an important marker of cardiovascular mortality and could be used as prognostic criteria in the determination of ventricular arrhythmia and sudden death [11]. Due to the effect of the anesthesia method and anaesthetics on the QT interval, together with several factors, and the fact that severe arrhythmia and mortality may be seen in the perioperative period, it is important for anesthetists to determine whether this period is extended by the drugs used [12]. The QT interval can be calculated using various formulae such as QT dispersion, which is the difference between the longest and shortest periods on ECG or corrected QT, which is corrected according to heart rate. It is still a matter of debate as to which parameters and which formulae provide the most correct results [13].

In this study, by examining the effect on the QTc interval of different doses of hyperbaric bupivacaine applied in elective inguinal hernia operations, we aimed to determine whether ventricular arrhythmia was caused and, in the light of the results obtained, to assess the safety of the doses of bupivacaine used. While there are previous studies in the literature showing the effect on the QT interval of different local anaesthetics in spinal anesthesia, to the best of our knowledge, no study has researched the effect of different doses of hyperbaric bupivacaine.

Material and Methods

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 and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Approval for the study was granted by the Scientific Research Ethics Committee of Kahramanmaras Sutcu Imam University Medical Faculty. The study included 60 patients, aged 19–43 years, ASA I-II status, who were to undergo elective inguinal hernia surgery in the General Surgery Department and accepted spinal anesthesia. Exclusion criteria were: refused regional anesthesia; blood clotting disorders; known allergy to the drugs to be used in the study; infection in the injection area which would prevent asepsis; rhythm disorder, cardiac disease, or long QT syndrome; using drugs which extend the QT interval; electrolyte disorders; and risk group of >ASA -II physical status. After the recording of preoperative ECG and hemodynamic baseline values, the patients were randomly allocated (by pulling numbered balls from a bag) to Group S1 (spinal block 1) or Group S2 (spinal block 2) before anesthesia was completed.

Non-invasive blood pressure (NIBP), heart beat rate, pulse oximetry (SpO$_2$), and 3-lead ECG monitorization were applied, then the baseline hemodynamic and demographic data (age, sex, weight, and height) were recorded. All the ECG data were recorded with a Nihon Kohden Cardiofax GEM ECG-9020 GEM (Tokyo, Japan) 12-derivation device. With the patient in a sitting position, the puncture area was disinfected. After sterile draping, the spinal block was applied by first entering the subarachnoid arachnoid space from the L3–L4 vertebral gap with a midline approach with a 25-gauge Quincke needle (B-Braun, Melsungen AG, Germany), then, when CSF flow was observed, the needle tip was adjusted to point downwards and 10 mg (2 ml) 0.5% Marcaine (Bupivacaine HCL 5 mg amp., Astra Zeneca, Germany) was applied to Group S1 and 15 mg (3 ml) was applied to Group S2. Following the injection, patients in both groups were placed in a supine position with the head raised at 30°. If systolic artery pressure (SAP) fell below 80 mmHg or mean arterial pressure below 60 mmHg, this was accepted as hypotension, and if IV fluid replacement did not improve this, a 5–10 mg ephedrine IV bolus was administered. If heart rate fell below 50 bpm, a 0.5-mg atropine IV bolus was administered. The non-invasive MAP and heart rate (HR) values were recorded before the spinal block and at 5 and 30 min after the block and at 60 min postoperatively. At the same time intervals, ECG was applied in all patients. In both groups, the time of the spinal sensory block to reach T10 dermatome was recorded as Anesth. T and the duration of the surgical procedure as Surg. T. On all the ECGs taken, the QTc interval was calculated using the Bazett formula [14]. A QT value of >440 msn was accepted as prolonged QT. For all patients, spinal anesthesia was applied by a single anesthetist and all the operations were performed by the same surgeon.

Table 1. Demographic data of the patients.

		Group			P value
		S1 (n=30)	S2 (n=30)	Total (N=60)	
Age*		29.4±6.80/42–19	29.9±6.29/43–19	29.7±6.50/43–19	0.754
Gender#					
	Female	9 (30.0)	7 (23.3)	16 (26.7)	0.771
	Male	21 (70.0)	23 (76.7)	44 (73.3)	
ASA#					
	I	25 (83.3)	23 (76.7)	48 (80.0)	0.741
	II	5 (16.7)	7 (23.3)	12 (20.0)	
Height* (cm)		170.6±5.66/178–158	171.4±5.37/180–157	171.0±5.49/180–157	0.577
Weight (kg)		73.8±8.85/87–55	75.3±8.10/89–58	74.6±8.45/89–55	0.472
AnaesT** (sec)		350 (400–340)	345 (400–340)	350 (400–340)	0.061
SurgT** (min)		32 (40–24)	32.5 (40–28)	32 (40–24)	0.464

Independent T test(Bootstrap) – Mann Whitney U Test (Monte Carlo) – Fisher Exact Test (Exact); * Mean±standard deviation/Maximum–Minimum; **Median (Maximum–Minimum); # n(%) A value of p<0.05 was accepted as statistical significance.

In the statistical analysis of the data, SPSS 23.0 (IBM Corporation, Armonk, New York, USA) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001-Paleontological statistics) programs were used. The conformity to normal distribution of data with a single variable was tested with the Lilliefors corrected Kolmogorov-Smirnov test, and in data with multiple variables we used the Mardia test (Dornik and Hansen omnibus) with the variance homogeneity Levene test. In the comparison of 2 independent groups, the independent samples *t* test with Bootstrap results and the Mann-Whitney U test with the Monte Carlo simulation technique were used. To examine the interaction according to groups of dependent variables, the general linear model repeated ANOVA test was used, and for post hoc analysis we used the Bonferroni test. In the comparison of categorical data, the Fisher exact test was applied. In the tables, quantitative data are expressed as mean ± standard deviation (SD) and median range (minimum-maximum), while categorical data are expressed as number (n) and percentage (%). Data were examined in a 95% confidence interval. A value of p<0.05 was accepted as statistically significant.

Results

No statistically significant difference was determined between the S1 and S2 groups in the demographic data of the patients

(age, sex, height, weight, and ASA) (p=0.754, p=0771, p=0.741, p=0.577, and p=0.472, respectively). The female/male ratio in Group S1 was 9/21 and in Group S2 it was 7/23. No statistically significant difference was determined between the S1 and S2 groups regarding Anaesth. T and Surg. T (p=0.061, p=0.464) (Table 1).

No statistically significant difference in QTc interval durations was determined between the S1 and S2 groups at baseline (QTc 1) or at 1 h after the operation (QTc4) (p=0.925, p=0.300). A statistically significant difference was determined between the values at 5 min after spinal block (QTc2) and 30 min after spinal block (QTc 3) (p=0.001, p=0.001). The QTc 2 and QTc3 values in Group S2 were found to be statistically significantly longer (p<0.001). No statistically significant difference was determined between the QTc4 and the QTc1 values in either group (p=1.000, p=0.679) (Table 2).

No statistically significant difference in heart rate values was determined between the S1 and S2 groups at baseline (HR1), 5 min after spinal block (HR2), and at 1 h after the operation (HR4) (p=0.274, p=0.129, p=0.214). A statistically significant difference was determined between the heart rate values at 30 min after spinal block (HR3) (p=0.010). The HR3 values in Group 2 were lower. When the HR values were examined within each group, no statistically significant difference was found

Table 2. Comparison of the QTc interval between and within the groups.

| | | Group | | | P value[1] |
		S1 (n=30)	S2 (n=30)	Total (N=60)	
QTc					
	1	399.3±9.75	399.6±9.28	399.5±9.44	0.925
	2	407.2±4.93	415.2±8.50	411.2±8.53	0.001
	3	415.8±5.44	432.3±6.99	424.1±11.60	0.001
	4	400.8±5.61	402.7±8.42	401.8±7.16	0.300
Difference					
	(1–2)	−7.9±9.79	−15.6±6.31	−11.8±9.52	0.001
	(1–3)	−16.5±9.71	−32.7±11.25	−24.6±14.22	0.001
	(1–4)	−1.5±10.56	−3.1±4.28	−2.3±8.04	0.416
	(2–3)	−8.6±6.25	−17.1±10.98	−12.9±10.06	0.001
	(2–4)	6.4±7.59	12.5±6.36	9.5±8.04	0.001
	(3–4)	15.0±7.22	29.6±10.50	22.3±12.56	0.001
P value[2]		<0,001	<0.001	<0.001	
	1→2	<0.001	<0.001	<0.001	
	1→3	<0.001	<0.001	<0.001	
	1→4	1	0.679	1	
	2→3	<0.001	<0.001	<0.001	
	2→4	0.031	<0.001	<0.001	
	3→4	<0.001	<0.001	<0.001	

General Linear Model Two-Way ANOVA(Univariate) (Method: Bootsrap) Post Hoc Test: Bonferroni. P value[1] – p value for the change between groups of variables; P value [2]: p value for the change within the group of variables; A value of $p < 0.05$ was accepted as statistically significant.

between any values in Group S1 (p=1.000). In Group S2, the HR2 and HR3 values were significantly lower than the HR1 values (p=0.007, p<0.001). No statistically significant difference was determined between the HR4 and HR1 values (p=1.000) (Table 3).

In the comparison of the MAP values, no statistically significant difference was determined between the S1 and S2 groups at baseline (MAP1) and at 1 h after the operation (MAP4) (p=0.435, p=0.516). A statistically significant difference was determined between the MAP2 and MAP3 values (p=0.001, p=0.002). In Group S2, the MAP values were lower. In Group S1 the MAP2, MAP3, and MAP4 values were significantly lower than the MAP1 values (p<0.001, p<0.001, p=0.006). No statistically significant difference was determined between the MAP2, MAP3, and MAP4 values (p=1.000). In Group S2, the MAP values at all measured times were significantly lower than the baseline MAP1 value (p<0.001). A statistically significant difference was determined between the MAP2, MAP3, and MAP4 values (p<0.001). The lowest values were found to be MAP2, MAP3, MAP4 (Table 4).

No severe hypotension, bradycardia, or arrhythmia requiring intervention was determined in any patient of either group throughout the operation.

Discussion

The results of this study show that when the spinal anesthesia QT interval lengthened, the effect associated with the dose of bupivacaine increased but caused no serious dysrhythmia.

Dysrhythmias in the perioperative period may occur for several reasons, and the drugs used in relation to the selected type of anesthesia and the changes in the autonomic nervous system play a major role. The combination of local anesthetic myocardial depressive effects with the blockage of the sympathetic nervous system in spinal anesthesia further increases the creation of arrhythmia [2,3]. In a study on the incidence of arrhythmia in spinal anesthesia, a high rate (70%) was observed and the majority of arrhythmias were found to

Table 3. Comparison of the heart rate (HR) values between and within the groups.

| | | Group | | | P value[1] |
		S1 (n=30)	S2 (n=30)	Total (N=60)	
HR					
	1	74.1±7.67	76.5±9.33	75.3±8.56	0.274
	2	72.7±7.40	69.9±6.86	71.3±7.21	0.129
	3	73.3±11.00	66.8±5.10	70.0±9.10	0.010
	4	74.3±7.42	76.7±7.16	75.5±7.32	0.214
Difference					
	(1–2)	1.4±7.32	6.7±10.14	4.0±9.16	0.030
	(1–3)	0.8±8.69	9.7±7.65	5.3±9.28	0.001
	(1–4)	−0.2±5.30	−0.2±7.01	−0.2±6.16	0.967
	(2–3)	−0.6±6.39	3.1±6.61	1.3±6.70	0.035
	(2–4)	−1.6±6.63	−6.8±8.79	−4.2±8.15	0.016
	(3–4)	−1.1±7.36	−9.9±5.94	−5.5±7.99	0.001
P value[2]		0,639	<0.001	<0.001	
	1→2	1	0.007	0.007	
	1→3	1	<0.001	<0.001	
	1→4	1	1	1	
	2→3	1	0.100	0.923	
	2→4	1	0.001	0.001	
	3→4	1	<0.001	<0.001	

General Linear Model Two-Way ANOVA(Univariate) (Method: Bootsrap) Post Hoc Test: Bonferroni. P value[1]: p value for the change between groups of variables; P value[2]: p value for the change within the group of variables; A value of $p<0.05$ was accepted as statistically significant.

be of a minor type. In the same study, when the types of arrhythmia were examined, the most frequent type was sinus arrhythmia (30.3%) followed by premature beats (27.2%) [15]. In recent years, monitoring of the QT interval has gained importance as an accepted prognostic factor in the formation of dysrhythmias, and it shows depolarization and repolarization of the ventricles [11]. The prolongation formed in this period increases the frequency of severe dysrhythmias such as ventricular fibrillation and polymorphic ventricular tachycardia (Torsades de pointes) [16].

Rather than the calculation of a single QT interval, the calculation of QT dispersion (QTd) or QT corrected according to heart rate (QTc) has been reported to be more accurate as there is no homogenization of the total repolarization of the heart. There is no consensus on the frequency of use of the QTd and QTc parameters or of the superiority of one over the other, and both have been used [17]. In the present study, the QTc parameter was evaluated, and in the calculation, the Bazett formula was used with the study guideline of Charbit et al. [14], which has

been shown to be able to define the QT and QTc interval with a very small margin of error. Owczuk et al. applied spinal anesthesia in orthopedic surgery to patients with no cardiovascular pathology and reported that QTc was prolonged with 0.5% hyperbaric bupivacaine and no serious cardiac arrhythmia occurred [18]. Similarly, in the current study, the QTc durations in the groups receiving 10 mg and 15 mg bupivacaine were observed to lengthen, starting from 5 min after spinal block and increased up to 30 min, and this was greater with the use of 15 mg bupivacaine. At 1 h after the operation, when the QTc values returned to the pre-block values, arrhythmia was not seen to have developed in any patient.

In animal studies of bupivacaine used in spinal anesthesia, the cardiotoxic effects have been found to be greater than those of other local anaesthetics [19,20]. Although it is not known why bupivacaine causes severe arrhythmias (e.g., supraventricular tachycardia, atrioventricular block, premature ventricular beat, and ventricular fibrillation) even at low doses, this effect is created at higher concentrations [3,21]. Therefore,

Table 4. Comparison of the mean arterial pressure (MAP) values between and within the groups.

		Group			P value[1]
		S1 (n=30)	S2 (n=30)	Total (N=60)	
MAP					
	1	84.9±8.30	86.2±8.11	85.6±8.56	0.435
	2	75.4±6.30	67.6±5.79	71.5±7.15	0.001
	3	75.8±4.73	71.4±4.45	73.6±5.08	0.002
	4	76.6±4.61	75.9±3.63	76.3±4.13	0.516
Difference					
	(1–2)	9.5±4.35	18.6±5.76	14.1±8.29	0.001
	(1–3)	9.1±5.33	14.8±6.04	11.9±7.48	0.001
	(1–4)	8.3±6.46	10.3±6.95	9.3±7.31	0.002
	(2–3)	−0.5±4.43	−3.8±2.79	−2.1±4.03	0.003
	(2–4)	−1.2±5.00	−8.3±5.18	−4.8±6.17	0.001
	(3–4)	−0.8±3.88	−4.5±4.18	−2.6±4.42	0.001
P value[2]		<0.001	<0.001	<0.001	
	1→2	<0.001	<0.001	<0.001	
	1→3	<0.001	<0.001	<0.001	
	1→4	0.006	<0.001	<0.001	
	2→3	1	<0.001	0.001	
	2→4	1	<0.001	<0.001	
	3→4	1	<0.001	<0.001	

General Linear Model Two-Way ANOVA(Univariate) (Method: Bootsrap) Post Hoc Test: Bonferroni. P value[1]: p value for the change between groups of variables; P value[2]: p value for the change within the group of variables; A value of $p<0.05$ was accepted as statistically significant.

changes in the sympathetic nervous system seem to be more prominent in the formation of arrhythmia. Previous studies have reported that the activation of the sympathetic nervous system in general, or regional anesthesia, causes the lengthening of the QT interval, which increases the risk of arrhythmia [22,23]. Although lengthening of the QT interval seems to be contrary to the formation of sympathetic blockage in spinal anesthesia, it may be explained by the level of the sympathetic blockage. When the level of sympathetic blockage does not exceed T5, especially in lumbar sympathetic blockage (i.e., when T1–T4 cardioaccelerator sympathetic nerve fibers are not affected), these fibers are stimulated after a period as compensation, which increases sympathetic activation, and this can lengthen the QTc [10,24].

As the sympathetic block is expected to be high in caesarean section operations, it is therefore no surprise that this activation could be less. This view is supported by studies reporting that spinal anesthesia must be applied safely in caesarean operations on pregnant patients with congenital long QT syndrome [25,26]. In the current study, the block level in inguinal hernia surgery was not expected to be as high as in caesareans. In Group S1 (in which 10 mg bupivacaine was used) the QTc lengthening starting at 5 min. The fact that there was not a great change in heart rate with time may be due to thoracic compensatory sympathetic activation. Although the QTc duration was longer in Group S2 (which received the higher dose of bupivacaine) than in Group S1, the lower heart beat rate showed that the number of cardioaccelerator fibers affected was proportional to the block level. Therefore, it can be considered that the lengthening of QTc in Group S2 occurred with the direct myocardial depression created by the increased dose of bupivacaine. When the MAP values were examined, the values were seen to have fallen in direct proportion to the sympathetic blockage, as expected, following the block in both groups. That fact that hypotension was deeper in Group S2 (in which the higher dose was used) is consistent with results in the literature and likely occurred due to higher sympathetic blockage preventing compensatory sympathetic activation [24].

A limitation of the present study is that the final sensory and motor block levels in the patients before surgery were not examined, and only the length of time the sensory block took to reach T10 dermatome was determined. Therefore, evidence could not be fully shown of the mechanisms explaining the lengthening of the QTc interval in spinal anesthesia.

Conclusions

In spinal anesthesia applied with different doses of hyperbaric bupivacaine in inguinal hernia operations, the QTc interval lengthened in a dose-dependent manner, but as the doses used did not cause any severe arrhythmia, they can be considered safe for use.

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