Original Article

The effect of subarachnoid or epidural bupivacaine on the QTc and P-wave dispersion

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Abstract

Aim: Bupivacaine, which is widely used in neuraxial anesthesia, may lead to negative inotropic effect and arrhythmias. In this study, our objective is to evaluate the effects of bupivacaine on corrected QT interval (QTc) and P wave dispersion in epidural anesthesia and to compare them with those in spinal anesthesia.

Material and Methods: Ninety patients (59 male, 31 female) who applied neuraxial anesthesia for unilateral inguinal hernia repair were randomly allocated into two groups: Group S (Spinal, n = 49), Group E (Epidural, n = 41). Neuraxial anesthesia was performed by bupivacaine in both groups. We calculated heart rate, QT interval, corrected QT interval and P wave dispersion from electrocardiography, before anesthesia and after the operation.

Results: Postoperative QT interval was significantly longer than preoperative value in both groups (preoperative 0.388 sec in Group S and Group E versus, postoperative 0.407 sec in Group S and 0.397 sec in Group E), (p=0.001). Postoperative QTc prolongation was significantly higher in Group S, but there was no statistically significant difference between the groups (preoperative 0.418 sec versus, postoperative 0.424 sec in Group S), (p = 0.129). Preoperative and postoperative P wave dispersion value revealed no statistically significant differences in both inter- and intragroup comparisons.

Conclusion: Bupivacaine caused a postoperative QTc interval prolongation in spinal and epidural anesthesia, which did not reach levels that were regarded as risky for ventricular arrhythmias despite being more prominent in the spinal anesthesia group compared with the epidural anesthesia group.

Keywords: Anesthesia epidural; anesthesia spinal; bupivacaine; QTc

INTRODUCTION

Cardiac arrhythmia is a common problem that is emerged during anesthesia procedure, and an important reason for morbidity and mortality (1). In general anesthesia, arrhythmia could originate from the effects of induction and intubation on the autonomous nervous system and the catecholamine discharge (2,3). In central neuraxial blocks, sympathetic blockade or direct cardiotoxic effects of the local anesthetics could elicit rhythm disorders, including even cardiac arrest (4). Bupivacaine, which is widely used in neuraxial blockades, may lead to negative inotropic effect and arrhythmias by blocking sodium channels and creating signaling defect (5). Bupivacaine may cause widening in QRS complex, prolongation in P-R and QT interval, A-V block, and ventricular arrhythmias on electrocardiogram (ECG), as well as hypotension and bradycardia (6,7). The QT interval, a recognized prognostic factor for ventricular arrhythmias if prolonged, and is defined as the gap starting from the beginning of the QRS complex to the end of T-wave on ECG which shows depolarization and repolarization of the ventricles (8). It may alter by several factors including age, sex, and heart rate. Corrected QT (QTc) interval is the QT value that is adjusted according to the heart rate (or mean heart rate 60/minutes in some formulas). Though many formulae could be used for this correction, Bazett's formula described in 1918 is still the most common calculation method: $QTc = QT \times \sqrt{RR}$ (9)

QTc prolongation is associated with increased risk of ventricular arrhythmias that may cause polymorphic ventricular tachycardia (torsades de pointes) and ventricular fibrillation (10). Prolongation of QTc interval was reported to be a significant biomarker of cardiovascular mortality and a probable prognostic factor for ventricular arrhythmia and sudden death (11).

P-wave dispersion (PWD), which is used as a non-invasive biomarker of atrial arrhythmias such as atrial flutter or atrial fibrillation, is defined as the difference

between maximal and minimal P-wave durations on ECG. While the first part of the P wave shows the right atrial depolarization, the second half shows the left atrial depolarization (8,12,13).

Although several studies reported QTc interval prolongation effects of bupivacaine in spinal anesthesia, the effects of this agent on PWD and its effects during epidural anesthesia have not been adequately studied. The aim of this study was to assess the effects of bupivacaine on QTc and PWD when used in epidural anesthesia and to compare them with those in spinal anesthesia.

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 the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. İnformed consent was obtained from all individual participants included in the study.

This cross-sectional study was conducted in the city of Elazig, state of Turkey and it was approved by the local ethics committee (date: August 11, 2015; approval number: 2015-15-09). The study included 90 patients, aged 19-65 years, ASA I-II status, who underwent to unilateral inguinal hernia repair and accepted central neuraxial anesthesia. Exclusion criteria were; refused central neuraxial anesthesia, blood clotting disorders, known allergy to the drugs to be used in the study, rhythm disorder, congenital or acquired QTc interval prolongation, patients taking medications that had any effect on the QTc interval (e.g. tricyclic antidepressants, antiarrhythmic, b-adrenergic antagonists or calcium channel blockers), serum electrolyte (potassium, magnesium and calcium) abnormalities.

Preoperative echocardiographic evaluation was performed to determine if any cardiac pathology was present in all of the patients. The patients were randomly allocated into two groups: Group S (Spinal, n = 49), Group E (epidural, n = 41). None of the patients received premedication. Following their admission into the operation room, ECG monitorization was performed and their first ECG records were taken. In Group S, spinal anesthesia was performed by delivering 2 ml 0.5 % bupivacaine with a 25-gauge Quincke needle to the L3-4 or L4-5 space via the midline approach to the patients in the sitting position. In Group E, epidural anesthesia was performed by using a Touhy 18 G needle, and a loss of resistance technique with sterile 0.9% NaCl solution to the L3-4 or L4-5 space via the midline approach to the patients in the sitting position. When the epidural space was defined, a catheter was placed inside when ensure appropriate catheter location, 10 ml 0.5% bupivacaine solution was administered. Following the injections, patients were placed in a supine position with the head raised at 300. Sensory block was evaluated with pinprick test, while motor block was assessed with the

Bromage scale. Surgery was allowed when the sensory block reached the T10 level.

Additional fluid loading and stabilization of hemodynamics with 5 mg ephedrine were planned for patients where blood pressure values fell 20% below control values; 0.5 mg iv atropine was planned for patients whose heart rate fell below 50 beats/min, and these patients were excluded from the study. Twelve leads of ECG recordings were performed before anesthesia and after the operation. We calculated heart rate using mean RR time. The QT interval was determined as between the beginning of QRS complex and the point where T waves descend onto the TP isoelectric line. The QTc interval was calculated using the Bazett formula. The beginning of P-wave was defined as positive deflection from the isoelectric line, and the endpoint when the positive deflection returned the isoelectric line. P-wave dispersion was the difference between the longest and shortest P-wave durations.

Statistical analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) version 20. Data distribution was analyzed using the analysis of variance. Parametric datas were expressed as the mean ± standard deviation. The effects of spinal and epidural anesthesia on preoperative QT, QTc and PWD and postoperative QT, QTc and PWD were evaluated using paired sample t-test. Differences between spinal and epidural anesthesia in QT, QTc and PWD were compared by means of unpaired Student's t-test. For all analyses, P<0.05 was accepted as evidence of significance.

RESULTS

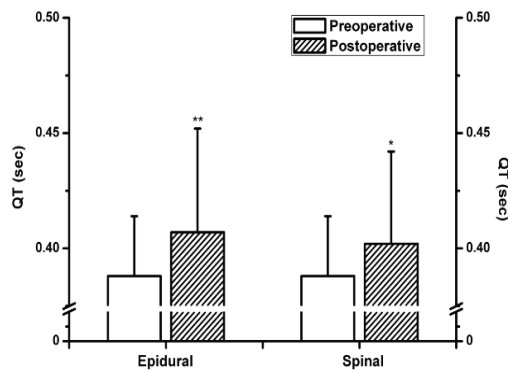| Table 1. Demographic characteristics of groups		
Demographic Characteristics	Group S (n=49)	Group E (n=41)
Age (Year)	50.1±3.3	57.21±3.2
Sex (M/F)	31/18	28/13
ASA I/II	21/28	11/30
Operation time (min)	45.3	48.2
Bupivacaine dose (ml)	2	10
ASA: American Society of Anesthesiologists (No significant differences in demographic characteristics were found between the groups)		

No significant differences in demographic characteristics were found between the groups (Table 1). The study groups did not statistically differ with respect to the preoperative echocardiographic parameters. Those patients with abnormal findings on echocardiography were excluded from the study (Table 2). Both groups showed decreased postoperative heart rate compared with that recorded in the preoperative period, yet no significant difference was found between the groups (Table 3). Both groups had significantly postoperative QT prolongation. Although it was more prolonged in Group S, the comparison

of the groups did not show the statistical difference (Figure 1). QTc was detected to be more prolonged in Group E and Group S during postoperative period. While the prolongation was significantly higher in Group S, there was no statistically significant difference between the groups (Figure 2). Preoperative and postoperative P max, P min, and PWD values revealed no statistically significant differences in both inter- and intragroup comparisons (Figure 3).

Table 2. Echocardiographic data of groups			
Parameters	Group S (n=49)	Group E (n=41)	p
EF (%)	59.57 ± 0.66	58.46 ± 0.56	0.21
LVESD (mm)	30.75 ± 0.34	30.56 ± 0.46	0.73
LVEDD (mm)	45.73 ± 0.37	45.58 ± 0.49	0.80
LA (mm)	33.61 ± 0.68	34.26 ± 0.42	0.43
IVS (mm)	10.32 ± 0.10	10.41 ± 0.10	0.56
EF: Ejection Fraction, LVESD: Left Ventricular end Systolic Diameter, LVEDD: Left Ventricular end Diastolic Diameter, LA: Left Atrium Diameter, IVS: Interventricular Septum			

Table 3. Preoperative and postoperative electrocardiographic data of groups			
Parameters	Group S (n=49)	Group E (n=41)	p
Preoperative HR (beats/min)	73.73 ± 13.71	73.82 ± 12.27	0.97
Postoperative HR (beats/min)	69.91 ± 14.35	70.97 ± 12.77	0.71
Preoperative QT interval (sec)	0.388 ± 0.02	0.388 ± 0.02	0.94
Postoperative QT interval (sec)	0.407 ± 0.04	0.397 ± 0.03	0.25
Preoperative QTc interval (sec)	0.418 ± 0.02	0.422 ± 0.02	0.45
Postoperative QTc interval (sec)	0.424 ± 0.02	0.422 ± 0.03	0.76
Preoperative P max (sec)	108.77 ± 14.08	105.85 ± 14.99	0.34
Postoperative P max (sec)	105.71 ± 15.27	106.09 ± 14.29	0.90
Preoperative P min (sec)	58.97 ± 17.22	56.09 ± 16.41	0.42
Postoperative P min(sec)	56.93 ± 16.48	55.60 ± 15.33	0.69
Preoperative PWD (sec)	49.79 ± 15.87	49.75 ± 15.08	0.99
Postoperative PWD (sec)	48.36 ± 15.59	50.24 ± 13.32	0.54

**Postoperative QT compared with Preoperative QT in spinal group (p=0.006); *Postoperative QT compared with Preoperative QT in epidural group (p=0.072)

Figure 1. The Effect of Subarachnoid or Epidural Bupivacaine on QT interval
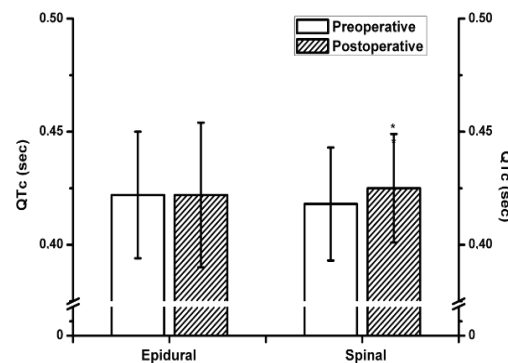
* Postoperative QTc compared with Preoperative QTc in spinal group (p=0.035)

Figure 2. The Effect of Subarachnoid or Epidural Bupivacaine on QTc interval
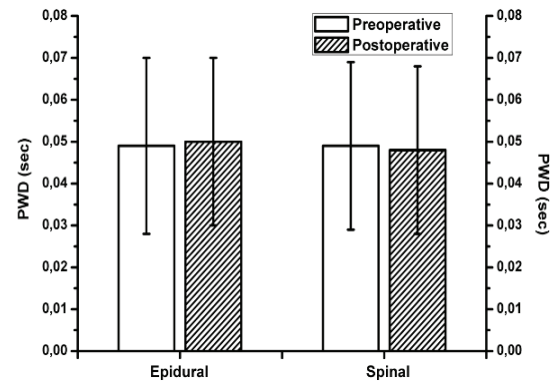

Figure 3. The Effect of Subarachnoid or Epidural Bupivacaine on PWD

DISCUSSION

This study showed that bupivacaine used in epidural and spinal anesthesia led to prolongation of QTc interval without influencing P wd in patients with no cardiovascular disease and that while being associated with a more marked prolongation in spinal anesthesia group, it did not cause a clinically serious arrhythmia in either group. The factors influencing QT interval include diabetes mellitus, ischemic heart disease, pulmonary disease, uremia, electrolyte and acid/base imbalance, and several medications such as antihypertensive agents, beta blockers, antidiabetics, or opioids. Therefore, the underlying etiology of QT prolongation is typically not easy to distinguish. Nevertheless, it should be identified on ECG due to the potential risk of developing serious ventricular arrhythmias (14).

The drugs used for general anesthesia or central neuraxial blockades or consequent sympathetic stimulation may affect QT interval. Inhalation anesthetics such as sevoflurane, desflurane, isoflurane and halothane were investigated regarding their effects on QT interval, and some studies reported sevoflurane to prolong QT interval, others advocated no change in QT interval with no difference between these agents (15-17). In the study which showed prolonged QTc interval by volatile induction and maintenance anesthesia with sevoflurane, selective spinal anesthesia with bupivacaine was reported not to alter QTc interval (2). In a multi-centered study, 70.2% of 17.000 patients that were administered spinal anesthesia were reported to have tachycardia, bradycardia, or arrhythmia (18). On the other hand, orthopedic surgery patients who received spinal anesthesia with 0.5% bupivacaine were shown to have prolonged QTc, although no serious cardiac arrhythmias (19).

The normal duration of QT interval ranges from 350 to 440 msec. For the QTc interval, as calculated by Bazett's formula, the values below 420 msec are accepted as normal, those between 420 and 440 msec as borderline long, and those values above 440 msec as high, while the latter possesses a serious risk for arrhythmias (8,9,20). Although both groups in our study were detected to have a prolonged QTc interval, no serious arrhythmia was observed probably because of no patient having a QTc interval above 440 msec.

Prolongation of QTc interval during spinal anesthesia is associated with sympathetic activation and the level of sympathetic blockade, rather than the effect of the anesthetic agent (21,22). If the blockade level does not exceed T5 in lumbar sympathetic block especially (i.e. when T1-T3 cardio-accelerating sympathetic fibers remains unaffected), these fibers become stimulated during compensation phase, causing sympathetic activation and QTc prolongation (22,23). Since this activation will not occur in cesarean procedures where sympathetic blockade is expected to be performed at higher levels, spinal anesthesia can be safely applied for the cesarean operations of women with congenital long QT syndromes (24,25). The QTc prolongation that was observed in our study could be attributed to the fact our study population included unilateral inguinal hernia repair operations where the sympathetic block level was lower than that required for a cesarean procedure.

Many toxic reactions of bupivacaine which is frequently used for central neuraxial blockades is associated with its higher plasma concentrations. 2 µg/ml plasma concentrations of bupivacaine were reported to cause a negative inotropic effect and prolonged cardiac conduction (5). In a study where 10 mg and 15 mg of bupivacaine doses were compared in spinal anesthesia, QTc interval was reported to be more prolonged in the high-dose group though plasma concentrations were not measured (26). Since our purpose in this study was to evaluate the effects of sympathetic activation elicited by spinal anesthesia and epidural anesthesia on QTc interval rather than the dose of the drug, we used lowest possible dose of bupivacaine as 10 mg in the spinal anesthesia group and 50 mg in the epidural anesthesia group.

As we intended to assess both ventricular and atrial arrhythmia risk, we measured not only QTc interval but also PWD. The association between atrial fibrillation episodes and PWD in patients undergoing cardiac surgery indicates that this parameter could be used to assess the risk of supraventricular cardiac arrhythmia. Chandy et al. reported that PWD was postoperatively prolonged in coronary artery bypass graft surgery patients, which was closely associated with atrial fibrillation episodes (12). Beta-blocker agents were reported to reduce PWD values in patients with cardiac disease (27,28).

On the other hand, PWD was shown to be elevated in anxiety and cardiac syndrome X cases that were associated with increased sympathetic system tonus (28,29). In a study investigating cardiac effects of thoracic and lumbar epidural anesthesia, PWD were found to be unchanged in both groups, which was attributed by the authors to the incapability of epidural anesthesia about eliciting a complete sympathetic blockade (30). P-wave dispersion was either not elevated in cesarean patients receiving spinal anesthesia. Consistently, we also did not observe any alteration in PWD value in epidural and spinal anesthesia groups.

This study has limitations. There were only two ECG recordings preoperatively and postoperatively. Postoperative ECG recordings defined the length of the prolongation in the groups. Holter monitoring could have provided information about heart rate variability.

CONCLUSION

This study demonstrated that bupivacaine use in spinal or epidural anesthesia caused a postoperative QTc interval prolongation, which did not reach levels that were regarded as risky for ventricular arrhythmias despite being more prominent in the spinal anesthesia group compared with the epidural anesthesia group. In addition, this study is the first to show the absence of any effect of spinal or epidural anesthesia on PWD, a biomarker of the atrial arrhythmia.

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