

# The Effects of Spinal Anesthesia on QT Interval in Preeclamptic Patients

Selda Sen, MD\*  
Galip Ozmert, MD†  
Hakan Turan, MD‡  
Eray Caliskan, MD‡  
Alper Onbasili, MD‡  
Duran Kaya, MD§

In this study, we measured the effects of spinal anesthesia on the corrected QT (QTc) interval in women with severe preeclampsia. Twenty-five preeclamptic (preeclamptic group) and 25 healthy pregnant women with normal arterial blood pressure and QTc interval (control group) were enrolled in this prospective, case-controlled study. Arterial blood pressure, heart rate, and QTc interval values were obtained before (baseline value) and at 5, 10, 20, 30, 60, and 120 min after initiation of spinal anesthesia. Total ephedrine dose, time elapsed until sensory block, and Apgar scores were recorded. Prior to spinal anesthesia, QTc interval values were significantly higher in the preeclamptic group ( $452 \pm 17.5$  ms) when compared with that in controls ( $376 \pm 21.4$  ms). Although the QTc interval shortened during spinal anesthesia when compared with baseline value in the preeclamptic group ( $P < 0.05$ ), it showed no significant change in the control group. In conclusion, the QTc interval may be prolonged in severe preeclamptic patients who have hypertension and hypocalcemia. Spinal anesthesia for cesarean delivery may normalize that prolonged QTc interval due to sympathetic blockade. (Anesth Analg 2006;103:1250-5)

**T**he QT interval, a marker of ventricular repolarization and prolonged QT syndrome, is diagnosed when this value is more than 440 ms (1). A prolonged QT interval can cause serious cardiac rhythm problems such as ventricular tachydysrhythmias (VT). VT can either revert spontaneously to sinus rhythm, producing syncope or pseudo seizures in its wake, or deteriorate into malignant dysrhythmia, ventricular fibrillation, and sudden death (Torsade de pointes) (2,3). Long QT syndrome (LQTS) can be congenital or acquired (1). Drugs, female sex, electrolyte imbalances (such as hypocalcemia or hypomagnesemia), and some neurological, cardiac and metabolic disorders can precipitate acquired LQTS (1,3).

The autonomic nervous system may also influence the QT interval corrected for heart rate (corrected QT interval, QTc). Abnormal sympathetic modulation or vagal withdrawal may directly alter ventricular repolarization, leading to prolonged QT interval (4).

Preeclampsia is defined as the development of hypertension with proteinuria after the 20th wk of pregnancy (5). The principal cardiovascular changes

in preeclamptic patients are increased sympathetic hyperactivity and systemic vascular resistance (6,7).

Neuroaxial blockade, such as epidural or spinal anesthesia, has been shown to modulate the effects of the stress response and sympathetic overactivity in preeclamptic patients (7,8). Therefore, we postulate that spinal anesthesia may have beneficial effects on prolonged QTc intervals due to sympathetic blockade.

In our clinical practice, we frequently observe QTc interval prolongation in severe preeclamptic patients who require urgent cesarean delivery. We designed this prospective, case-controlled study to investigate the effects of spinal anesthesia on prolonged QTc interval in patients with severe preeclampsia.

## METHODS

After obtaining approval of the institutional ethical committee and informed patient consent, 25 severe preeclamptic (preeclamptic group) and 25 healthy pregnant women (control group), who were scheduled for urgent cesarean delivery were enrolled in this study. The 25 severely preeclamptic pregnant women who fulfilled the inclusion criteria were selected from 312 preeclamptic patients, who were admitted to our institution between 1999 and 2001.

For the preeclamptic women, inclusion criteria were the diagnosis of severe preeclampsia and a history of arterial normal blood pressure values in the first 20 wk of gestation. Exclusion criteria included a history of cardiovascular disease, primary hypertension, connective tissue disease, diabetes mellitus, or medications that could affect QT interval and fetal structural abnormalities. Severe preeclampsia was defined as arterial blood pressures more than 160/110 mm

From the Departments of \*Anaesthesiology and ‡Cardiology, Adnan Menderes University, Aydin, Turkey; †Department of Obstetric and Gynecology, SSK Ankara Maternity and Women's Health Teaching Hospital; and §Department of Internal Medicine, Ankara University, Ankara, Turkey.

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Address correspondence and reprint requests to Selda Sen, MD, Adnan Menderes Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon A.D., 09100 Aydin, Turkey. Address e-mail to drseldasen@yahoo.com.

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Hg on two or more occasions at least 6 h apart during bed rest, and proteinuria more than 5 g or more of protein in a 24-h urine collection, or 3+ or more on urine dipstick testing of two random urine samples collected at least 4 h apart. The other criteria for the diagnosis of severe preeclampsia were oliguria (<500 mL urine/24 h), pulmonary edema, impaired liver function, visual and cerebral disturbances, intrauterine growth restriction, and pain in the epigastric area or right upper quadrant, in addition to hypertension and proteinuria (5).

Control patients were healthy pregnant women with normal electrocardiograms (ECG) and no hypertension, proteinuria, or other systemic diseases.

A baseline 12-lead ECG was obtained in the preoperative holding area for all patients. At the time of arrival in the operating room, standard monitors were applied with an automatic blood pressure cuff, five-lead ECG, and pulse oximetry. The standard ECG lead II was continuously recorded and printed at a paper speed of 50 mm/s and an amplification of 0.1 mV/mm before and at 5, 10, 20, 30, 60, and 120 min after initiation of the spinal anesthesia. Systolic, diastolic, mean arterial blood pressures, oxygen saturation (SpO<sub>2</sub>), and heart rate values were also recorded at the same time intervals.

The two investigators who performed the ECG analysis were blinded to patient group. Heart rate was calculated from the three R-R intervals preceding the measured QT intervals. The QT intervals were measured manually from the onset of the QRS complexes to the end of the T wave (defined as the intersection of the isoelectric line and the tangent of the maximal downward limb of the T wave). Each registered measurement was a mean of two consecutive QT intervals. The measured QT interval was then corrected for heart rate, according to the formula of Bazette (9):

$$QTc = \text{Measured QT} / \sqrt{\text{RR interval}} \\ (\text{all measured in seconds}).$$

QT interval was accepted as "prolonged," when QTc values exceeded 440 ms.

Serum calcium (ionized and total) and magnesium (Mg) levels were measured immediately before surgery. All patients received 7–10 mL/kg lactated Ringer's solution just before spinal anesthesia, administered over 20 min. Spinal anesthesia was performed at the L3–4 or L4–5 spaces in the sitting position with 2.5 mL 0.5% hyperbaric. Lactated Ringer's solution 5–6 mL kg<sup>-1</sup> · hr<sup>-1</sup> and 500 mL hydroxyethyl starch (HES) 6% solution were infused together IV, as per our standard hospital practice, from the beginning of spinal anesthesia until completion of surgery. A decrease in systolic blood pressure more than 20% after spinal anesthesia was defined as hypotension. Hypotension was initially treated with fluid resuscitation. If the arterial blood pressure did not respond, ephedrine 5–10 mg was administered IV.

**Table 1.** Demographic Characteristics of the Study Groups and Duration of Surgery

	Preeclamptic group (n = 25)	Control group (n = 25)
Age (yr)	30.2 ± 6.7	28.8 ± 5.4
Weight (kg)	82.9 ± 16.1	79.7 ± 17.9
Gestational age (wk)	35.5 ± 1.5*	37.4 ± 1.7
Duration of surgery (min)	29.4 ± 6.7	32.5 ± 4.8

Data are shown as mean ± sd.

\* P = 0.029 for preeclamptic versus control group.

**Table 2.** Electrolyte Levels of the Study Groups

	Preeclamptic group (n = 25)	Control group (n = 25)
Total calcium (8.5–10.5 mg/dL)	8.1 ± 0.7*	9.8 ± 0.9
Ionized calcium (1.10–1.45 mmol/L)	0.87 ± 0.3†	1.12 ± 0.4
Magnesium (0.7–1 mmol/L)	0.88 ± 0.07	0.85 ± 0.05

Data are shown as mean ± sd.

\* P = 0.034 and † P = 0.041 for Preeclamptic versus control group.

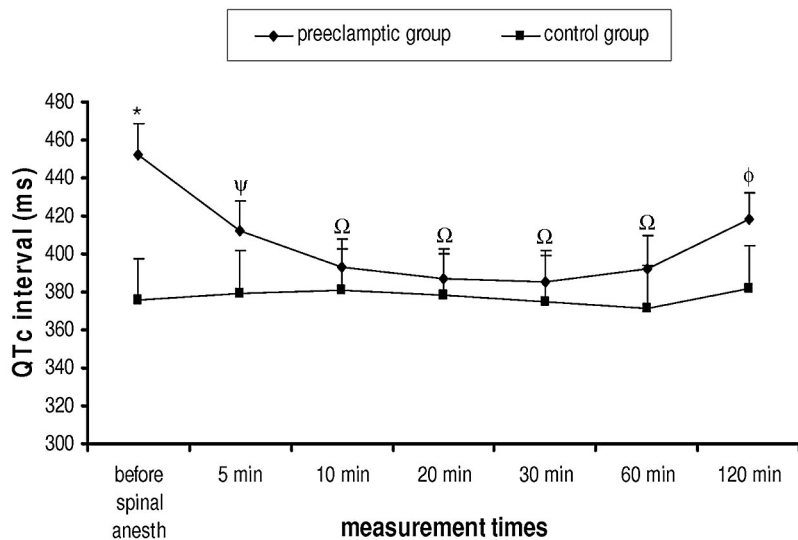
Onset time of motor block, total ephedrine dose, and Apgar scores of the newborns were also recorded in both groups. The time of maximal sensory block level (min) and regression to two segments (min) was also recorded.

At the time of arrival in the postanesthesia care unit (PACU), standard monitoring was applied with an automatic blood pressure cuff, three lead ECG, and pulse oximetry. We frequently evaluated QTc interval by ECG samples in the postoperative period. The effects of Mg therapy were evaluated frequently by monitoring hourly fluid balance, maternal heart rate, respiration/minute, deep tendon reflexes, and blood Mg levels.

### Statistical Analysis

The power of this study was calculated using the G Power analysis program (<http://www.physcho.uni-duesseldorf.de/aap/projects/gpower/index.html>). The statistical power of the matched analysis was computed in a pilot study that was performed previously (15 cases per group). In the pilot study, a change of at least 70% in the QTc interval during spinal anesthesia was accepted as significant. On the basis of these estimates, we calculated that a sample size of 25 patients per group would permit a type I error of  $\alpha = 0.05$  and power of 90%.

The data were expressed as means ± sd. Analysis of variance (ANOVA) was used for inter-group comparisons. When there were significant differences, Bonferroni correction was applied to detect the exact location between groups. For nonparametric data, the Mann–Whitney U-test was used.  $\chi^2$  analysis and Fisher's exact test were used to compare the side effects of



**Figure 1.** Alteration of corrected QT (QTc) intervals: Data are shown as mean  $\pm$  SD. QTc interval was recorded before (baseline value) and at the 5, 10, 20, 30, 60, and 120 min of the spinal anesthesia. \* $P < 0.0001$ , preeclamptic versus control group (baseline values).  $\Psi P = 0.0019$ , in preeclamptic group (5 min vs baseline value).  $\Omega P < 0.0001$ , in preeclamptic group (10, 20, 30, and 60 min vs baseline value).  $\phi P = 0.0024$ , in preeclamptic group (120 min vs baseline value).

anesthesia between the study groups.  $P < 0.05$  was considered as statistically significant.

## RESULTS

The demographic's of the two groups were not significantly different (Table 1). Mean gestational age as well as serum ionized and total calcium values were significantly lower in the preeclamptic group as compared to controls. ( $P < 0.05$ ) (Tables 1 and 2). Prolonged QTc interval was observed in 18 patients (72%) in the preeclamptic group before initiation of spinal anesthesia. Serum ionized and total calcium levels were less than normal limits in 14 (56%) patients of the preeclamptic group. No patient had a prolonged QT interval or electrolyte abnormality before spinal anesthesia in the control group. Mg treatment was not administered in the preeclamptic group because of the urgent need for delivery. IV Mg therapy was initiated after completion of surgery. The initial dose was an infusion of 6 g  $\text{MgSO}_4$  in 100 mL dextrose within 20 min followed by 2 g/h  $\text{MgSO}_4$  infusion until 24 h postpartum.

$\alpha$ -methyl dopa was administrated to 17 (68%) patients during the last trimester in the preeclamptic group for hypertension. All cesarean deliveries were urgent. Indications for cesarean delivery in the preeclamptic group were fetal distress, oligohydramnios, oliguria, acute increases of serum transaminases, and subjective maternal symptoms, including visual disturbances and epigastric pain. In the control group, cesarean delivery indications included multiple pregnancies, oligohydramnios, unfavorable Bishop score, malpresentation of the fetus on ultrasound examination, and meconium passage. Apgar scores were similar between the study groups.

The QTc interval value was significantly longer in the preeclamptic group ( $452 \pm 16.5$  ms) when compared with that in the control group before spinal anesthesia (baseline value) ( $378 \pm 22.4$  ms) ( $P < 0.0001$ ). QTc interval values were significantly shortened at 5, 10, 20, 30, 60, and 120 min when compared

with baseline values in the preeclamptic group, however, there were no significant changes in the control group at the same times (Fig. 1).

Mean arterial blood pressure values before the induction of spinal anesthesia were significantly higher in the preeclamptic group when compared with that in controls ( $P = 0.036$ ). Mean arterial blood pressure values decreased significantly in both the preeclamptic (24%) and control (26%) groups at 5 min, when compared with their baseline values ( $P = 0.043$ ). Sequential changes at other measurement times were not significantly different in either group. Of note, there were no significant differences at any measurement time between the two study groups regarding mean arterial blood pressure values (Fig. 2).

Heart rate values before spinal anesthesia were significantly higher in the preeclamptic group ( $P < 0.05$ ). While the heart rate values significantly decreased at 5, 10, 20, 30, and 60 min after spinal anesthesia in the preeclamptic group ( $P < 0.05$ ), a similar difference was not noted in the control group (Fig. 3).

Ephedrine was used in 11 (44%) patients in the preeclamptic group and 10 (40%) patients in the control group for the treatment of hypotension. Total ephedrine dosage during spinal anesthesia was similar in both groups ( $17.3 \pm 9.7$  and  $19.2 \pm 10.1$ , respectively).

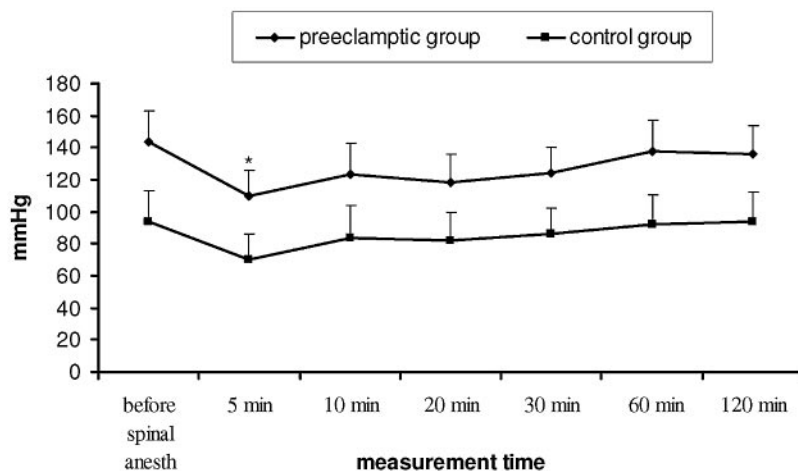
We did not find any significant differences between the study groups for maximal sensory block height, time of maximal sensory block level (min), regression to two segments (min), and the time elapsed until motor block (min) (Table 3).

We did not observe any complications such as significant changes in arterial blood pressure values, arrhythmias, or eclamptic seizures in either group during the first 24 postoperative hours and all patients were discharged without any complications.

## DISCUSSION

The main finding of this study was that QTc interval was more frequently prolonged in preeclamptic patients, probably because of hypertension and

**Figure 2.** Mean arterial blood pressure values. Data are shown as mean  $\pm$  SD. Mean arterial blood pressure values were recorded before (baseline value) and at the 5, 10, 20, 30, 60, and 120 min of the spinal anesthesia. \* $P = 0.036$ , in the preeclamptic group and  $P = 0.043$  in the control group (5 min vs baseline values).



hypocalcemia, when compared with that in the healthy pregnant women. Another finding was that spinal anesthesia might normalize the prolonged QTc intervals in these women, probably as a result of the sympathetic blockade.

Abnormalities of calcium and magnesium metabolism are well-known risk factors for QT interval prolongation (1,3,10). Mg regulates several cardiac ion channels, such as the calcium channel and outward potassium currents, through the delayed rectifier (10). IV Mg is regarded as the treatment of choice for immediate treatment of Torsade de pointes associated with the LQTS, regardless of the serum Mg level (3,10).

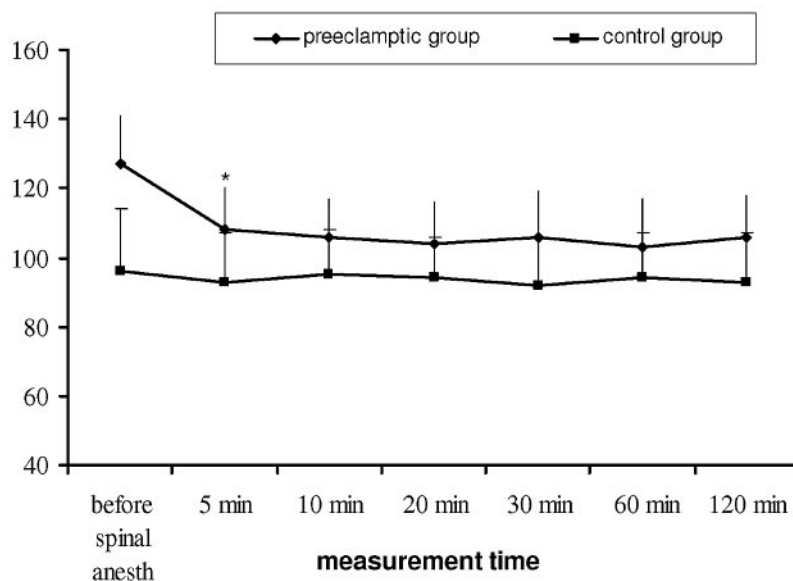
Mg therapy is clearly indicated for women with preeclampsia (7,11,12). It has been shown to decrease the incidence of eclampsia and is also likely to decrease overall mortality (11). The MAGPIE trial (12) was the largest trial to date examining hypertensive diseases in pregnancy, including preeclampsia. In this study, more than 10,000 women with preeclampsia were randomized to receive either Mg therapy or placebo, and the rate of eclampsia and the relative risk for

death were significantly lower in the Mg therapy group (12). Kisters and et al. (13) determined that there was no difference in the plasma Mg levels of preeclamptic and healthy pregnant women; however, in preeclamptic women, the red blood cell Mg level was lower. We also found that serum Mg levels were similar between study groups. In our study, Mg therapy was not administered to any patient in the severe preeclampsia group during either the preoperative or intraoperative period, but was started as an infusion immediately after surgery. We did not observe any complications, such as eclamptic seizures or arrhythmias, in these patients.

Although several studies have shown that both serum calcium and Mg levels in preeclamptic women were lower than in normal pregnant women (14,15), prolonged QT interval due to hypocalcemia has been reported in only one patient with eclampsia (16).

Hypocalcemia prolongs Phase 2 of the action potential, and thus prolongs repolarization time as inward Ca currents are one of the factors that influence the plateau configuration of the action potential (17). Although the ionized calcium level was slightly lower

**Figure 3.** Heart rate (bpm). Data are shown as mean  $\pm$  SD. Heart rate values were recorded before (baseline value) and at the 5, 10, 20, 30, 60, and 120 min of spinal anesthesia. \* $P = 0.039$ , in preeclamptic group (all others versus baseline value).



**Table 3.** Characteristics of Spinal Block

	Preeclamptic group (n = 25)	Control group (n = 25)
Time of maximal sensory block level (min)	7.5 ± 1.6	7.2 ± 1.9
Maximal sensory block height	T6	T5
Regression to two segments (min)	86.7 ± 4.3	83.4 ± 9.6
Time elapsed until motor block (min)	4.4 ± 1.7	4.7 ± 1.5

Data are shown as mean ± sd.

There was no significant difference between study groups.

than normal in the preeclamptic patients, we also measured calcium levels in the postoperative period and replacement therapy was administered, if necessary.

Hypertension can be associated with sympathetic and cholinergic imbalance characterized by vagal withdrawal and relative sympathetic dominance. Therefore, hypertension may trigger ventricular arrhythmias (18). The changes in autonomic nervous system activity can directly affect the conduction systems, causing variations on QT interval length independently from heart rate and may confound the clinical assessment of cardiac repolarization time (4,18).

Preeclampsia is associated with a state of sympathetic overactivity that usually reverts to normal after delivery (6,7,19). This sympathetic hyperactivity may lead to an increase in systemic vascular resistance and arterial blood pressure. This hyperactivity is seen three times more commonly in preeclamptic pregnant women when compared with those who are normotensive (19). Sympathetic hyperactivity, hypertension, and hypocalcemia, secondary to preeclampsia might have contributed to prolongation of the QT intervals of preeclamptic women in our study.

Patients with LQTS who present for anesthesia and surgery are at risk of developing malignant ventricular dysrhythmia and/or sudden death during the perioperative period (1,2). The management of anesthesia should continue to focus on prevention of excessive sympathetic activity and avoidance of factors that can prolong the QT interval (1,20). In several published case reports, spinal anesthesia has been safely used for cesarean delivery in pregnant women with long QT syndrome (21,22).

Ramanathan and Benneth (7) demonstrated that regional anesthesia might be more effective to reduce sympathetic activity compared with general anesthesia in severe preeclampsia. Furthermore, recent studies also suggest that spinal anesthesia can be safely used in the severely preeclamptic patient (23,24). In our study, the prolonged QT interval was back to normal value within 5 min after spinal anesthesia. This might also reflect a relationship between the sympathetic block and QTc interval.

Seventeen patients in the preeclamptic group received  $\alpha$ -methyl dopa during the last trimester of pregnancy. The effect of  $\alpha$  methyl dopa on the QT interval has not been reported, however, we believe that this antihypertensive medication did not affect the QT interval.

IV bolus oxytocin can cause a prominent and transient QTc interval prolongation and may lead to proarrhythmias (25). We did not administer bolus IV oxytocin to any of our patients, but instead, administered this drug by slow IV infusion. This, however, may have also contributed to prevention of QTc prolongation.

We conclude that close ECG monitoring is useful to determine the existence of prolonged QTc interval in severe preeclamptic patients who have hypertension and hypocalcemia. Spinal anesthesia during cesarean delivery may normalize prolonged QTc intervals in these women due to sympathetic blockade. Further research should be performed to evaluate the effects of various anesthesia techniques on the QTc interval in the patient with severe preeclampsia, and should include a longer period of postoperative follow up.

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