Changes on QT, QTc and P Dispersion during Flexible Bronchoscopy under Propofol and 12121 Remifentanil Sedation. A Double-Blind Randomized Trial

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Abstract

Background: Serious hemodynamic alterations have been shown during flexible fiberoptic bronchoscopy (FFB). QT and P wave dispersion (QTd, Pd) may give us an significant information about cardiac status during FFB. This study aimed to compare the effect of propofol and remifentanil sedation on QTd, corrected QT dispersion (QTcd) and Pd during FFB.

Method: Forty-nine ASA class I or II patients who were not pre-medicated were selected and allocated to receive either propofol 1 mg/kg (n=20) or remifentanil 1 µg/kg (n=20) and titrated to achieve Ramsey sedation score level of 5. QTd, QTcd and Pd were measured on electrocardiography baseline (T0), at the end of the infusion of drugs (T1), shortly after laryngoscopy (T2), at the end of bronchoscopy (T3) and the time of Modified Aldrete score to be achieved 10 (T4). Heart rate, mean arterial pressure, respiratory rate and partial CO2 pressure in blood gas were recorded at these time points. Furthermore, recovery times (RT) were recorded.

Results: QTd at all measurement times, corrected QTd at T1 and T2, P dispersion at T1, T2 and T3 increased significantly in the propofol group compared to remifentanil group (p<0.05). Mean arterial pressure increased significantly in the propofol group compared to the remifentanil group at T2 (p<0.05). There was a significant decrease in respiratory rate at T1 and T3 in the remifentanil group (p<0.05). There were no significant differences in heart rate and partial CO2 pressure between groups. RT was shorter in the remifentanil group (p<0.05).

Conclusion: Remifentanil shortened and propofol prolonged QTd, QTcd and Pd at sedative doses during FFB. Also we obtained the short RT with remifentanil. So remifentanil may be more suitable sedative agent during FFB.

Keywords: Flexible bronchoscopy; Propofol; Remifentanil; QT dispersion; P dispersion

Introduction

Although flexible fiberoptic bronchoscopic (FFB) examination is a relatively safe procedure, serious complications and deaths may occur. The sympathetic discharge and hypoxemia are common complications which may predispose to other problems, including cardiac dysrhythmias [1,2]. During FFB, major arrhythmia (rarely life-threatening) as 11%, myocardial ischemia as 17%, different cardiac dysrhythmias [1,2]. During FFB, major complications which may predispose to other problems, including QT dispersion (QTcd) and P wave dispersion (Pd) during FFB.

Numerous studies have identified QT dispersion (QTd) or corrected QT dispersion (QTcd) as a predictor of life-threatening arrhythmias and cardiovascular mortality [5,6]. It has been observed that the laryngoscopy and tracheal intubation associated with significant stimulation of sympathetic activity may cause a prolonged QTc interval during anesthetic induction in healthy patients [7]. Furthermore, it has been reported that the increased P wave dispersion (Ped) are connected with increased risk of atrial fibrillation [8,9].

Although there is no consensus related to the necessity of sedation during FFB, it may relieve anxiety and stress, improve patient comfort, and facilitate the bronchoscopic procedure [10,11]. Also, hemodynamic alterations such as tachycardia, hypertension induced by the sympathetic discharge may be prevented with sedation. But we should be careful to the hypoxemia due to the apnea induced by the sedative agents. Propofol was associated with lower hemodynamic side effects versus combined sedation in the patients undergoing FFB [12]. Although it was shown that propofol did not increase QT interval, prolongation of QT related to propofol was observed in some studies [13-15]. Several studies have shown that remifentanil attenuates the hemodynamic response to intubation and rigid bronchoscopy [16,17]. Kweon et al. [18] reported that remifentanil may prevent the QTc prolongation associated with tracheal intubation.

The effect of both propofol and remifentanil on QT or QTc dispersion were investigated during various procedures but not yet during FFB. Therefore the aim of this prospective, randomized and double-blind study was to investigate the effect of propofol and remifentanil sedation on the changes in QTd, QTcd and Pd during FFB.

Method

Patients

This study was approved by the Ethical Committee of Baskent University (Project no: KA09/392), Ankara, Turkey (Chairperson Prof. Dr. Eftal Yücel) on 03 December 2009. After obtaining written informed consent, 40 American Society of Anesthesiologists physical

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status (ASA I–II) who were between 40–75 years old consecutive patients undergoing diagnostic elective FFB were prospectively randomized utilizing a computer system in a double-blind fashion. Patient's exclusion criteria were preoperative QT and QTc of >440 ms, cardiac arrhythmias, using drugs prolong QT interval, severe coronary disease or heart failure. The patient’s characteristics (gender, age, weight, ASA status) were recorded.

Anesthesia and sedation

All patients arrived to the bronchoscopy unit without premedication. Topical anesthesia was performed with 5 mL of 2% lidocaine (100 mg of lidocaine) nebulizing for 15 minutes. Patients were sedated with propofol as 1 mg/kg (group P, n=20) or remifentanil as 1 µg/kg (group R, n=20) for 10 minutes intravenously (i.v.) infusion and drugs were titrated as 5 mg and 10 µg respectively to keep Ramsay sedation score (RSS, defined in Table 2) as 5 without creating respiratory depression.

The total doses of the sedative drugs were recorded. The anesthesiologist accompanied to the patients throughout the procedure, and managed the administration of the sedation and the monitoring of the patients. Patients were discharged from bronchoscopy unit when they achieved modified Aldrete score (MAS, defined in Table 2) [19] of 10.

Monitoring and ECG analysis

Monitoring during the FFB included peripheral oxygen saturation (SpO2), respiratory rate (RR), continuous ECG with 12 lead and managed the administration of the sedation and the monitoring of the patients. Patients were discharged from bronchoscopy unit when they achieved modified Aldrete score (MAS, defined in Table 2) as 5 without creating respiratory depression.

The results were expressed as numbers (n) or mean (SD). A p value <0.05 was considered significant. Sample size was determined on the basis of a pilot study (SD 15 ms), which indicated that, with 20 patients in each group, a power of 85% would be required to detect a difference

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| Parameter                | Description of patients | Score |
|--------------------------|-------------------------|-------|
| Activity                 | Moves 4 extremity voluntarily or on command | 2     |
|                          | Moves 4 extremity voluntarily or on command | 1     |
|                          | Unable to move any extremities | 0     |
| Respiration              | Able to deep breathe and cough freely | 2     |
|                          | Dyspnea or limited breathing | 1     |
|                          | Apnea | 0     |
| Circulation              | Blood pressure ≤ 20% of preanesthetic level | 2     |
|                          | Blood pressure 20–49% of preanesthetic level | 1     |
|                          | Blood pressure ≥ 50% of preanesthetic level | 0     |
| Consciousness            | Fully awake | 2     |
|                          | Arousable on calling | 1     |
|                          | Not responding | 0     |
| Peripheral oxygen saturation (SpO2) | Maintains SpO2>92% on room air | 2     |
|                          | O2 needed to maintain SpO2>90% | 1     |
|                          | SpO2<90% even with O2 supplement | 0     |

Table 2: Modified Aldrete score scale.
of 10 ms in the mean QTcd between two groups at a significance level of 0.01.

Results

In all patients, bronchoscopy was completed successfully. All patients achieved to 10 of MAS and discharged from bronchoscopy unit. Demographic characteristics were presented in Table 3. Further, there were no significant differences between groups related with the number of bronchoalveolar lavage and biopsy. Also, total doses of the drugs were showed in Table 3. Although there was no a significant differences in BT between groups, RT was longer significantly in group P than in group R (Table 3, p=0.007).

A bradycardia, hypotension or hypertension and the ischemic ST segment changes as defined in method section did not arise in any patients.

The patients had normal QTd, QTcd and Pd at rest, and there were no statistically significant differences among the baseline QTd, QTcd and Pd values of the both groups. Also there were no significant differences between groups in baseline HR, MAP RR and SpO2 values.

QTd was significantly longer in group P than group R at all times. (p=0.008, p=0.001, p=0.008, p=0.02 respectively, Figure 1). In group R, QTd intervals were decreased insignificantly at all times compared with baseline values (p>0.05). In group P, we observed a significant increase in QTd at T1 and T2 times compared with baseline values (p=0.05, p=0.004 respectively).

In group P, QTcd interval was significantly longer than group R at T1 and T2 (p=0.012, p=0.001 respectively, Figure 2). In group P, there were significant increases in QTcd at T1 and T2 compared with baseline value (p=0.016, p=0.028 respectively). QTcd interval decreased significantly at T2 compared with baseline value in group R (p=0.044).

There were significant differences in Pd interval at T1, T2 and T3 times between groups. In group P, Pd intervals at these times were significantly longer than group R. (p=0.004, p=0.025 respectively). The Pd significantly decreased at T1 (p=0.002) and increased at T2, T3 and T4 compared with baseline values.

In group P, QTd interval was significantly longer than group R at T1 and T2 (p=0.012, p=0.001 respectively, Figure 2). In group P, there were significant increases in QTd at T1 and T2 compared with baseline value (p=0.016, p=0.028 respectively). QTd interval decreased significantly at T2 compared with baseline value in group R (p=0.044).

There were significant differences in Pd interval at T1, T2 and T3 times between groups. In group P, Pd intervals were significantly longer than group R in these times. (p=0.00, p=0.001, p=0.023 respectively, Figure 3). Whereas Pd increased significantly at T1 and T2 in group P (p=0.007, p=0.01 respectively), it decreased significantly at T2 in group R compared with baseline values (p=0.035).

There were significant differences in the HR changes between groups. The values of the HR increased significantly at T2, T3, T4 in group P (p=0.01, p=0.001, p=0.005 respectively) and decreased at T1 in group R compared with the baseline (p=0.011).

The increase in the MAP at T2 was more significant in group P than group R (p=0.012, Figure 4). The MAP decreased significantly in group P at T1 (p=0.001), however it increased significantly at T2 and T3 compared with the baseline values (p=0.001, p=0.035 respectively). But there were no significant alterations in the MAP in group R compared with the baseline values.

There were significant differences in RR at T1 and T3 times between groups. In group P, RR intervals at these times were significantly longer than group R. (p=0.004, p=0.025 respectively). The RR significantly decreased at T1 (p=0.002) and increased at T2, T3 and T4 compared with baseline values.
with the baseline values in group R (p=0.003, p=0.001, p=0.001 respectively). However, in group P, RR did not decrease significantly after sedation. At T2, T3 and T4 times, RR increased significantly compared with the baseline values in group P (p=0.01, p=0.002, p=0.01 respectively). There were no significant differences between the groups in SpO2 (Figure 5). The SpO2 decreased significantly in both groups at T1 and T3 compared with the baseline values (p=0.02, p=0.004 in group P, p=0.01, p=0.005 in group R). There were no significant differences between the groups related to PCO2. PCO2 was found between 34.8-48.9 mmHg (39.8 ± 16.23) in group P, 35.2-49.2 mmHg (40.21 ± 21.42) in group R (Table 3).

**Discussion**

Although, the numerous studies were done in hemodynamic alterations during FFB, there are no published studies on the QTd, QTcd and Pd during FFB.

We observed that the QTd, QTcd and Pd were significantly prolonged in group P, and shortened in group R. Nevertheless, the increased QTd, QTcd and Pd returned to the baseline values at the end of recovery time and none of the patient showed a dangerous cardiac arrhythmia in group P.

In present study, QTd, QTcd or Pd changes were seen after both sedation and laryngoscopy. Presumably, QTd, QTcd or Pd changes occurred after laryngoscopy and sedative drug induction with different mechanisms. Authors reported that both laryngoscopy and intubation may cause an increasing in HR, blood pressure and plasma catecholamine concentration, then this high level of plasma catecholamine concentration may increase the after load of the heart and as a result the prolonged QT interval and cardiac arrhythmia can occur [7,20]. In a study, it was showed that the catecholamine infusion resulted in QT prolongation in normal subjects [21]. It is well documented that both propofol and remifentanil may cause a dose-dependent depression in cardiovascular system via sympathetic blockade. In our study, a decrease in the HR and MAP developed after the administration of sedative drugs, but an increase in the HR and MAP developed after laryngoscopy and during bronchoscopy. Although severe hypotension and bradycardia or tachyarrhythmia did not develop in both groups, an excessive variability in the HR and MAP were observed after both sedation and laryngoscopy in group P. This instability of hemodynamic status may be related to the inadequate sedation. However, we defined the dose of the sedative agent, according to the RSS in both groups and a similar sedation scores were found in both groups. In group R we obtained the better hemodynamic response.

It has been thought that hypoxemia increases the risks of tachyarrhythmia in patients affected by respiratory failure directly or increasing the sympathetic activity indirectly, which worsens the left ventricle performance [22]. In patients with chronic obstructive airway disease, hypoxia has been shown to cause an increase in QTd [23,24]. Hypoxemia is experienced frequently during FFB due to the bronchospasm, airway obstruction and hypoventilation. RR decreased more significantly after sedation in group R than group P but there is no significant difference in SpO2 between the groups. In both groups we observed a mild hypoxemia (SpO2 of 90% to 93%). It is possible that the mild hypoxemia can also cause sympathetic activity increase.

Actually we can not constitute the safety of airway completely during FFB due to the technical reasons of the procedure. Furthermore, we cannot suppress the sympathetic discharge perfectly because of the anesthetic agents are used in only sedative dose. These situations may increase the risk of hypoxemia and catecholamine discharge and may trigger the cardiac arrhythmia.

Hypercapnia has been blamed to prolong the QTc interval and QTd [25]. Egawa et al. [26] reported that QTd prolongation was connected to the longer duration of CO2 insufflation during laparoscopic cholecystectomy. In the present study, because of there were no significant differences between the groups relating with hypercapnia, we were not able to find such a relationship between hypercapnia and QTd, QTcd or Pd. Also there were no correlation between patients developed hypercapria and the prolongation of QTd, QTcd and Pd in group P.

In the myocardial cell membrane, the rate of repolarization of action potential are generally regulated with slowly and rapidly activating channels during phase 2 and 3 of the electrical cardiac cycle [27]. Although inhalation anesthetic agents prolong the QTc by blocking the rapidly activating channel independent from autonomic nervous system, the effect of opioids on potassium channels is not clear [28,29]. Katchman et al. [30] reported that a very high dose fentanyl can block cardiac human ether-a-go-go related gene currents. This report was consistent with Lischke's report [31] that the QT interval prolonged after injection of fentanyl in patients undergoing coronary artery bypass graft surgery. We can expect the similar effect for remifentanil due to the structurally unique with fentanyl, but we could not find a report describing the effects of remifentanil on potassium currents in previous studies. Remifentanil's short context sensitive half life and its rapid plasma effect site equilibration make the degree of analgesia precisely controllable. When compared with the propofol, the remifentanil produces more analgesic effect. This effect may help to reduce the sympathetic response caused by the painful stimuli of the laryngoscopy and broncoscopy. Remifentanil causes a dose-dependent decrease in HR, arterial blood pressure and cardiac output [32]. Although some studies showed that remifentanil had prevented the prolongation of the QT interval, it has not yet been used in adult FFB [18,27,33]. Reports concluded that the remifentanil provided effective sedation combined with propofol in children [34,35]. In our study, remifentanil (1 µg/kg bolus, total consumption 123 µg ± 48.02 mean/SD) did not increase QTd and QTcd interval. Kweon et al. [18] reported that remifentanil (1 µg/kg) prevented the QTc prolongation related to the intubation after sevoflurane induction. Another study reported that a continuous infusion of remifentanil (0.1 µg/kg/min) prevented the fatal arrhythmia in patients with a long QT syndrome [36]. In the other similar study, after 2 min of sevoflurane induction, remifentanil was given 0.25 µg/kg over a 30 sec period, then laryngeal mask airway was inserted and a prolongation in QTc interval was not seen [27]. They commented that the low dose of remifentanil prevented the prolongation in QTc,
because of the laryngeal mask airway insertion is far less stimulating than direct laryngoscopy and endotracheal intubation. In these studies, remifentanil was used with other anesthetics, but in the present study it was used alone. Therefore, we believe that the effect of remifentanil on QTd prolongation was evaluated more reliably. We obtained a moderate hemodynamic response, so QTd and QTCd prolongation were not seen in group R.

For the sedation during FFB, propofol is used frequently. It has some advantages as providing adjustable level of sedation, rapid recovery, unnecessary for antagonist agents [37]. Because of there is a wide variability in the response of the patients to the drug, it is necessary to acquire experience to adjust the dosage of propofol to the individual patient [38] Gonzalez et al. [39] showed that, when a propofol was administered under local anesthesia during FFB, the tolerance of the patient is much better as the evaluation by the patient and in the hemodynamic response. They used propofol a bolus of 0.5-1 mg/kg and titrated doses of 20 mg for maintenance to keep a stated level of sedation and SpO2. Although we used a similar dose of propofol, hemodynamic response was more exaggerated than group R. These changes may be responsible for prolonging of QTd and QTCd in group P. Nevertheless, no dangerous cardiac arrhythmia and myocardial ischemia finding were observed on these patients. Although there is a controversy about the effect of propofol on QTd prolongation, the reports showed that, it doesn't generally cause the QTd prolongation [13,14,40-42]. However, in these studies, it may be complicated to evaluate the effect of propofol on QTd prolongation, because many anesthetic drugs (including opioids and volatile anesthetics) which were administered with propofol may affect the QT interval.

Higashijima et al. [40] showed that propofol shortened the QTc interval after anesthesia induction and intubation. In this study fentanyl was used for anesthesia induction with propofol and the patients were not exposed to over sympathetic discharge. But the other studies observed that propofol prolonged QT or QTc interval minimally after endotracheal intubation [41,42]. As we mentioned above, an excessive sympathetic discharge occurs during bronchoscopy. So, in our study, the increase in QTd and QTCd may be related with the sympathetic discharge was not depressed adequately with propofol. Although an adequate sedation level was obtained, the sympathetic discharge could not be prevented sufficiently with the actual dose of a propofol in our study. Erdil et al. [14] used propofol as a sedative dose (1 mg/kg), but the QT interval did not increase and the better hemodynamic response was obtained during electroconvulsive therapy. During electroconvulsive therapy a balanced autonomic response may be obtained due to the parasympathetic response may develop together with sympathetic discharge. So heart rate variability may be useful to evaluate the autonomous nerve system in this situations [43]. Heath et al. [44] reported that propofol may alter the ion channel in the myocardium which could have an effect on the QTc interval, due to the delayed rectifier potassium current. Several studies showed that PD has a predictive value for atrial fibrillation in patients without apparent heart disease [8,9]. To our knowledge, this study is the first one in investigation PD during FFB. Furthermore, there are small number of study on the effect of anesthetic agents to the P wave interval or PD. Tukek et al. [45] have reported that an increased sympathetic activity causes a significant increase in PD. Owczuk et al. [46] reported that PD interval shortened significantly with propofol (2.5 mg/kg bolus and continued with infusion). They observed that propofol decreased PD interval, due to the anti-arrhythmic properties of the drug. In our study, PD interval prolonged in group P in a similar way of QT and QTc prolongation. As mentioned before, it is possible that the sympathetic discharge could not be depressed in our study due to the administration of propofol or an excessive sympathetic discharge during FFB. Propofol is known to suppress supraventricular tachycardia [47-50]. Such effects of propofol are associated with suppression of sympathetic tonus, increase in vagal tonus, changes in baroreceptor reflex sensitivity, and its effects on atrioventricular transmission [51]. Although we believe that remifentanil shortened PD with the same way as in QTd or QTCd in our study, we were not aware of previous studies describing the effects of remifentanil on PD.

Although there is no a consensus in the necessity of sedation during FFB between authors, for most patients, bronchoscopy is associated with anxiety, fear of pain and breathing difficulties [52]. Therefore, the majority of the patients prefer to be sedated during this procedure [52,53]. Furthermore, sedation may also make the procedure easier for the bronchoscopist to perform and the patient more desirous to accept a repeat procedure [54]. Because of both propofol and remifentanil have a rapid onset effect and short acting, they are generally used for sedation during short procedures. In present study, group R patients achieved earlier than 10 of MAS than group P. Authors reported that patients were given remifentanil had rapid recovery [55-57]. In a study, prolonged discharge time was observed in remifentanil due to the nausea during extracorporeal shock wave lithotripsy [58]. In this study, lithotripsy probably triggered the nausea. In the present study, nausea and vomiting did not develop.

In the present study 3 points were examined firstly; the first one is QTd, QTCd and PD analysis during FFB, the second one is using the remifentanil during FFB and the third one is the effect of remifentanil on PD.

The limitation of this study was the absence of control group. But in our clinic, we ethically do not want to perform FFB without sedation. This study may guide for the future researches in patients with long QT syndrome to perform FFB under sedation.

In conclusion, the bronchoscopic procedures affect the heart due to the significant stimulation of sympathetic activity and hypoxemia. So, the selected sedative drugs should not cause an additional stress factor causes a prolongation of QT dispersion. This case may not be a problem in healthy patients but, severe arrhythmias may occur in old patients with prolonged QT dispersion. Remifentanil shortened and propofol prolonged QTd, QTc and PD at sedative doses during FFB, fortunately dangerous arrhythmias were not observed. Also we observed that short RT with remifentanil. Remifentanil may be more suitable sedative agent for patients with congenital long QT syndrome and in the presence of other agents or factors that lengthen QT during FFB.

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