

Electrocardiographic Changes after Neostigmine-Atropine Mixture

Giovani Lock*, Guilherme Loureiro Fialho, Daniel Castro Lima and Maria Cristina Simões Almeida

Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil

Introduction

Neostigmine is the most widely used drug to antagonize neuromuscular block. However, the anticholinesteratic effect of neostigmine is not exclusive of the neuromuscular junction and muscarinic systemic effects like bronchoconstriction and bradyarrhythmias are expected after its administration [1]. Atropine, a non-specific muscarinic antagonist, is used to attenuate its side-effects [2]. This association may alter the autonomic control of the heart and increase QT interval. Long QT interval predisposes to ventricular arrhythmias which may degenerate to ventricular fibrillation and sudden cardiac arrest and death [3-5].

This prospective study was conducted to determine whether the mixture neostigmine-atropine causes significant changes in electrocardiographic intervals and heart rate. It was also addressed if these changes are dose-dependent.

Methods

After the local ethics committee approval and written consent was obtained by all patients, we studied 58 physical status (ASA) I-III adults patients who were scheduled for surgery under general anesthesia in which neuromuscular block was indicated. Patients were not included when they were pregnant, older than 65 years or obese (Body Mass Index greater than 30 kg.m⁻²). Patients suffering from cardiac, renal or hepatic disease; those with pre-operative electrocardiographic abnormality or those in chronic use of drugs causing blood pressure or heart rate changes were not included as well.

Patients received 1-3 mg of midazolam on arrival in the operating theatre. A venous cannula was inserted into the forearm for infusion of crystalloids. A multi-parameter monitor was installed and electrocardiogram on derivations DII and V5, automated arterial blood pressure, peripheral arterial oxygen saturation and capnography were monitored throughout the study. Electrocardiographic traces were printed intermittently with a specific device (FUNBEC, São Paulo; Brazil).

Acceleromyography was used to monitor neuromuscular blockade in the arm opposite to the blood pressure monitor. The acceleration transducer was fixed to the volar side of the thumb and a constant preload was applied. The response of the *adductor pollicis* muscle to ulnar nerve stimulation in the wrist was recorded using TOF Watch-SX® (Organon Technika). Acceleromyography was calibrated in the pre-programmed "Cal" mode immediately before neuromuscular block.

Anesthesia was induced with propofol 2-3 mg.kg⁻¹ and infusion of remifentanyl 0, 1-0,5 µg.kg⁻¹.min⁻¹ and was maintained with remifentanyl and sevoflurane (maximum 2%) in Oxygen-Air. Rocuronium 0, 6 mg.kg⁻¹ was used to facilitate orotracheal intubation and bolus of 10 mg were used as clinically needed. All patients were mechanically ventilated to obtain EtCO₂ between 30-35 mmHg and prophylaxis of post-operative vomiting consisted of ondansetron 8 mg and dexamethasone 10 mg.

At the end of the surgery, patients were assigned to the following two groups according to the train-of-four (TOF) ratio: Group I – patients with 0,2 < TOF < 0,7 received 0,04 mg.kg⁻¹ of neostigmine and

0,02 mg.kg⁻¹ of atropine; Group II – patients with 0,7 ≤ TOF < 0,9 received 0,02 mg.kg⁻¹ de neostigmine and 0,01 mg.kg⁻¹ of atropine. Patients who presented TOF < 0, 2 at the end of the surgery were kept sedated and ventilated until spontaneous recovery to TOF > 0,2 and were allocated then to Group I.

Data was recorded at the following moments: before anesthesia, before neostigmine-atropine injection, two, five and ten minutes after neostigmine-atropine injection. Reversion was considered successful when TOF > 0, 9. After recovery of spontaneous breathing, patients were extubated and admitted in the recovery room for routine care.

Electrocardiographic measurements included determination of PR, RR and QT intervals in derivations DII and V5 by a cardiologist who was blind to patient's allocation. The greater value was used in statistical analysis. Heart rate was calculated using the formula: HR=60÷RR. PR interval was defined as the time between the start of the P wave to the beginning of the QRS complex; PR changes were adjusted for Heart Rate (PRa) according to the formulae reported by Soliman [6]. RR interval was defined as the interval from the onset of one QRS complex to the onset of the next QRS complex. QT interval was defined as the time between the start of the Q wave and the end of the T wave. The QT interval was also adjusted to improve the detection of patients at increased risk of ventricular arrhythmia using Framingham's formula: QTc=QT+0,154(1-RR), where QTc is the QT interval corrected for heart rate, and RR is the RR interval measured in seconds.

The standard deviation of increase in QTc after anticholinesteratics was assumed to be of 11 mseconds. [7] Based on this fact, a sample size of 12 patients per group would be needed to detect an increase in QTc of 20, 2 mseconds, accepting an alpha error of 0, 05 and a beta error of 0, 2. An increase of 20 mseconds was considered clinically significant because US Food and Drug Administration recommends that drugs that cause increase in QTc interval greater than 20 mseconds should be monitored to cardiac events during implementation tests [3]. To prevent a loss of cases due to non-adherence to the protocol, a final sample of 15 subjects was used in each group.

To analyze the association between categorical variables the chi-square test was used. To analyze differences between means the student's *t*-test was used. Analysis Of Variance for Repeated Measures was applied to detect differences Between-Subjects according to group and also to detect differences Within-Subjects in time points (with Greenhouse-Geisser correction and Pairwise Comparisons). Data is

*Corresponding author: Giovani Lock, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil; E-mail: giovanielocks@gmail.com

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shown as mean ± standard deviation or frequency (percentage). A p < 0, 05 was considered significant.

Results

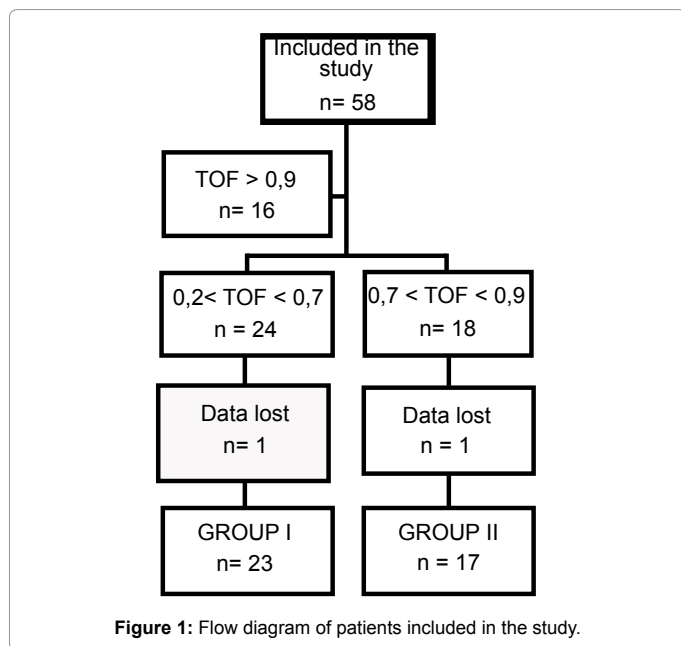
From July 2009 to April 2010, 58 patients were enrolled in the study. 16 were excluded because of spontaneous recovery of neuromuscular function, i.e., TOF > 0, 9 at the end of the surgery. Two patients were also excluded because of impossibility of registering electrocardiographic data integrally, one in each group. The final sample consisted of 23 patients in Group I and 17 patients in Group II. (Figure 1)

No significant difference in demographic data, physical status or BMI was noted between groups. (Table 1)

Surgery time and total doses administered of rocuronium were greater in Group I in relation to Group II. (Table 2) Neuromuscular block was successfully reversed (TOF > 0, 9) in all patients.

There were no differences between groups regarding electrocardiographic data on pre-anesthetic measurement (Table 3).

There were no cases of adverse cardiac events. There were increases in Heart Rate in the second minute after administration of neostigmine



	Group I	Group II	p
Genre (Male/Female)	12 (52%) / 11 (48%)	5 (29%) / 12 (71%)	0,18
Age (years)	42,4 ± 11,2	38,2 ± 11,4	0,26
ASA Physical Status (I/II-III)	10 (43%) / 13 (57%)	6 (35%) / 11 (65%)	0,93
Body Mass Index (kg/m2)	25,1 ± 3,7	26,3 ± 2,8	0,29

Table 1: Demographic data, physical status and Body Mass Index in both groups.

	Group I	Group II	p
Duration of surgery (min)	142,50 ± 71,97	91,87 ± 41,82	0,009
Propofol (mg)	202,17 ± 34,50	182,35 ± 63,49	0,106
Remifentanil (mg)	3,00 ± 3,46	1,87 ± 0,34	0,102
Rocuronium (mg)	53,33 ± 15,83	43,23 ± 12,74	0,020

Table 2: Anesthetic and surgical data in both groups.

	Group I	Group II	p
Heart Rate (bpm)	78,4 ± 11,9	78,5 ± 9,3	0,99
PR (sec)	0,167 ± 0,01	0,166 ± 0,01	0,55
QT (sec)	0,372 ± 0,02	0,383 ± 0,02	0,11
QTc (sec)	0,422 ± 0,02	0,422 ± 0,02	0,78

Table 3: Electrocardiographic data on pre-anesthetic measurement in both groups.

-atropine mixture in both groups (p < 0, 001 but with no difference between groups (p < 0, 54). There were no modifications in PR between moments (p < 0, 32) or between groups (p < 0, 12). Decrease of PRa was noted in the second minute (p < 0, 006) but with no difference between groups (p < 0, 15). Decrease of QT interval was noted in the second minute (p < 0, 008) but with no difference between groups (p < 0, 31). There were no modifications in QTc nor between moments (p < 0, 10) neither between groups (p < 0, 48) (Figure 2).

Discussion

The most important finding of this study is that 0, 04 mg.kg⁻¹ of neostigmine plus 0, 02 mg.kg⁻¹ of atropine or 0, 02 mg.kg⁻¹ of neostigmine plus 0, 01 mg.kg⁻¹ of atropine caused no significant changes in QT or QTc intervals.

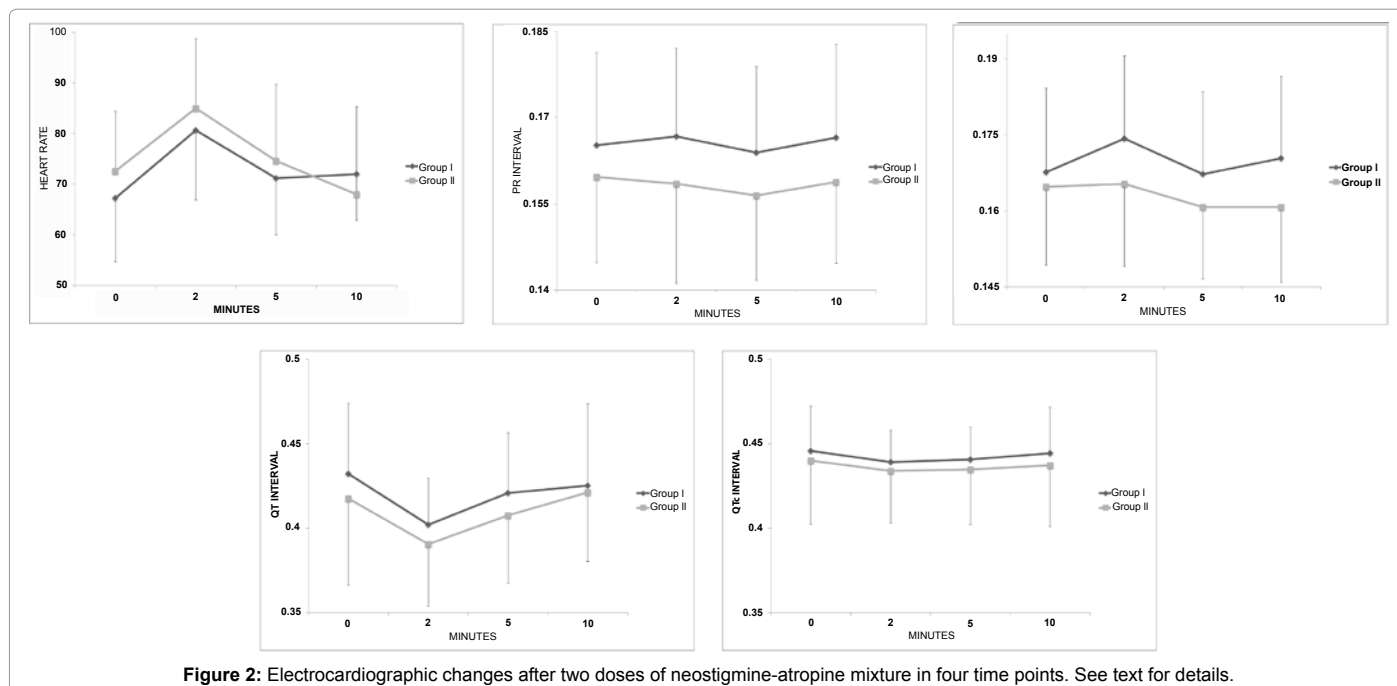
Because of the influence of heart rate in the QT interval it is commonly adjusted. Several formulas have been proposed, and recent recommendations argue in favor of non linear formula like Framingham. However, it is not clear if the appearance of disrhythmias is more related to QT or QTc interval, but most authors consider QTc more adequate to estimate cardiac risk. Proarrhythmic drugs usually increases both [3]. Despite the exact increase of QT or QTc interval in which there is a greater risk of arrhythmias is not established, drugs that augment QT or QTc interval more than 20 mseconds have a great potential of proarrhythmic effect.

The length of QTc interval that predisposes patients to sudden cardiac death is dependent of gender. Long QTc interval (>450 mseconds for men and >470 mseconds for women) was associated to a threefold increased risk of sudden cardiac death [8]. This issue was not addressed in this study, but a qualitative analysis showed that QTc interval was greater than these limits for at least two consecutive time points in 41% of men and 39% of women (data not shown).

Several drugs may increase QT or QTc interval and predispose to Torsades de Pointes (TdP), like disopiramide, dofetilide, ibutilide, procainamide, quinidine, sotalol and biperidil. Other drugs may cause TdP depending on individual predisposition: amiodarone, arsenic, cisapride, methadone, calcium channel blockers, droperidol, domperidone, chlorpromazine and haloperidol [5]. (See also: International registry for drug-induced arrhythmias. University of Arizona Center for Education and Research on Therapeutics; www.qt drugs.org, Accessed October15th 2010)

Drugs commonly used in anesthesia have also the potential to increase QT interval length like thionembuthal, ketamine, isoflurane, sevoflurane, succinylcholine, pancuronium, sufentanil, neostigmine, edrofonium, atropine, glicopirrolate, epinephrine and norepinephrine [4].

Reports from as early as 1949 include deaths and cardiac events among complications after anticholinesterasics-anticholinergic use [9-12]. Adverse cardiac events were noted in conditions of cardiac disautonomy, like in heart transplanted subjects [13-15]. Ventricular fibrillation was seen in healthy young patients who found out previously



unrecognized cardiac disease (one patient had Long QT syndrome and the other one had mitral valve prolapse) [16,17]. Coronary vasospasm, represented by the elevation of the ST segment two minutes after administration of neostigmine-atropine, figure in the literature [18]. Some events after reversal of neuromuscular blocks have no identified cause [19].

In our study, PRa changes after atropine-neostigmine have been noted. In a critical analysis these changes were considered not clinically significant, albeit statistically significant (Pra 0, 17 versus 0, 16 sec). The prognostic significance of the rate-adjusted PR still needs to be investigated [6].

One limitation of this study is the fact that electrocardiographic measurements were done manually. We have tried to attenuate this effect blinding the observer to group and moment allocation.

Most of the information about cardiac events of reversal of neuromuscular block was established from case series/reports. Investigations on this topic were not homogeneous and their clinical significance is hard to know [7,20-22].

Some issues addressed in this study, even though they are not in the focus of this work deserve to be pointed out. From all studied patients, 72, 5% needed neuromuscular block reversal at the end of the surgery. In 29,3% TOF ratio was between 0,7 and 0,9. If these patients were evaluated exclusively by clinical methods they could not be candidates to reversal of neuromuscular block and might be at risk of postoperative residual neuromuscular block. This data confirms the work of other authors and reinforces the need of an objective method to evaluate the degree of neuromuscular block in the moment of taking the decision of reversing or not the non-depolarizing block [23].

Despite the side effects of each drug, and reports of adverse events after the administration of anticholinesterasics-anticholinergics, this study showed that their use is relatively safe. These drugs have been largely used for more than half-century due to their incontestable cost-benefit. Vigilance of the electrocardiogram, however, should be taken because of their potential proarrhythmic effect.

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