EFFECTS OF ORAL CLONIDINE PREMEDICATION ON PATTERN OF HEART RATE AND BLOOD PRESSURE CHANGES AFTER NEOSTIGMINE-ATROPINE ADMINISTRATION

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SUMMARY : Injection of Neostigmine-Atropine mixture (N-A) may cause tachycardia, cardiac dysrrythmia and ischemia. This study was designed to determine effects of oral clonidine premedication on pattern and desirability of heart rate (HR) and mean arterial blood pressure (MAP) changes after N-A injection.

In this double blind randomized clinical trial study, 80 adult patients without cardiovascular disorders who were scheduled for elective surgery of orthopedics, gynecology, and laparotomy were assigned to receive approximately 5μ g/kg oral clonidine (clonidine group, n=40) 90 minutes before induction of general anaesthesia. At the completion of surgeries, Neostigmine-Atropine mixture was administered and HR and MAP values were measured noninvasively at 1 minute interval for 10 minutes and at the 20th minute after N-A injection. The control group was also compared of 40 patients and were delt exactly the same except clonidine administration.

In clonidine group, absolute values of HR changes after N-A injection were significantly less than that of the control group whereas absolute values of MAP changes were similar in two groups. Changes of HR and MAP after N-A injection were linear in both groups. In clonidine group, slope of HR changes 1 to 10 minutes after N-A injection was less than the control group (-2.09 vs. –2.72).

It seems that preoperative clonidine preserves basal parasympathetic nervous activity at the time the study drugs are injected.

Key Words: Clonidine, Neostigmine-Atropine, General anaesthesia.

INTRODUCTION

Injection of Neostigmine-Atropine mixture (N-A, reversal) causes transient tachycardia, premature atrial contraction, Wenckebach phenomenon, Junctional rhythm, inverted p-wave, atrioventricular dissociation, premature ventricular contraction and cardiac arrest. Many of cardiac complications following reversal occur during emergence of anaesthesia when a change in concentration of inhaled anaesthesia, surgical stimulation and ventilation causes cardiac arrhythmias. Inci-

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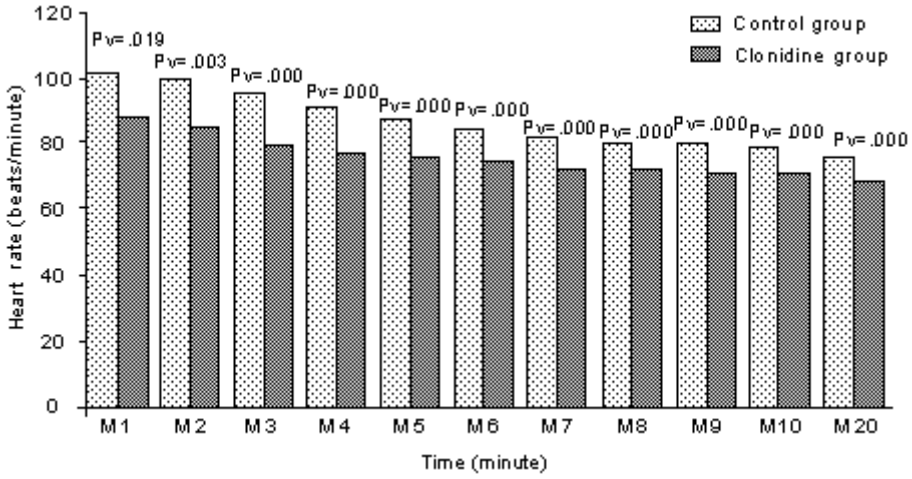
Figure 1: Comparison of postreversal 1 to 20 minutes heart rate changes in two groups. (M=Minute after reversal).



dence of cardiac dysrrythmia following neostigmine is higher in elderly patients with cardiovascular disease (1).

Injection of N-A mixture impairs cardiac baroreflex sensitivity (BRS) and high frequency component of heart rate variability (HRV) in early postoperative period thus leading to increase cardiac arrhythmia and decrease survival after myocardial infarction (2). Indices of parasympathetic modulation of HR are impaired for at least 120 minutes postoperatively after N-A, and neostigmine does not prevent inhibition of BRS (2). It is therefore desirable to maintain intact parasympathetic modulation of HR that results in decreasing incidence of myocardial ischemia during early postoperative periods (2). Postoperative ischemic episodes are associated with tachycardia which and as HR, occurs simultaneously with incidence of ischemia is highest ischemia (3).

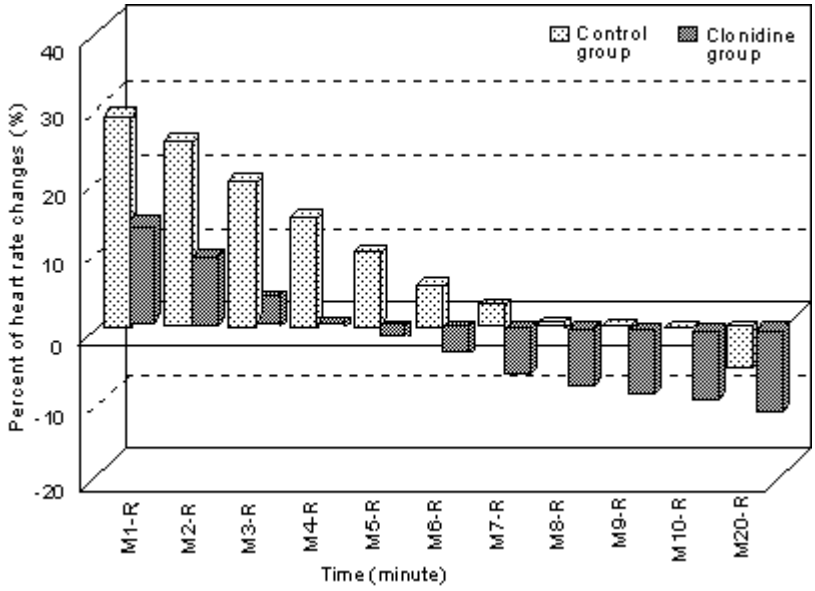
Considering complications of N-A, it seems prudent to use methods to counteract these complications effectively. These methods include hyperventilation for creation of mild respiratory alkalosis, co-administration of N-A in 2.5/1 ratio (4) and slow injection of them (2-5 min), maintenance of enough oxygenation during N-A injection (1) and reduction in dosage of atropine or replacement of it by Glycopyrrolate (5,6).

Table 1: Heart rate and mean arterial blood pressure values after Neostigmine-Atropine injection in the clonidine and control groups.

Min. PoR		1	2	3	4	5	6	7	8	9	10	20
Control (n=40)	MAP	98 ± 11	99 ± 11	96 ± 11	94 ± 19	99 ± 11	94 ± 10	92 ± 10	90 ± 10	89 ± 11	89 ± 11	87 ± 12
	HR	104 ± 19	101 ± 19	97 ± 19	93 ± 16	89 ± 16	86 ± 18	84 ± 18	88 ± 19	82 ± 20	81 ± 18	77 ± 14
Clonidine (n=40)	MAP	97 ± 17	96 ± 11	93 ± 11	90 ± 11	89 ± 11	87 ± 10	87 ± 10	88 ± 91	88 ± 13	85 ± 9	82 ± 12
	HR	90 ± 15*	86 ± 16*	82 ± 15*	79 ± 16*	78 ± 16*	76 ± 16*	74 ± 14*	73 ± 14*	72 ± 14*	72 ± 14*	70 ± 13*

- Values are mean ± SD
- HR = heart rate (beats/min)
- * P < 0.05 versus control group
- MAP = mean arterial blood pressure (mmHg)
- Min. PoR = minute postreversal

Figure 2: Percentage of postreversal heart rate changes relative to the baseline values in two groups. (M-R = Minute-rest, p<0.05 for M1-R to M5-R).



Studies done on clonidine, Rave revealed that it, as an α_2-agonist, decreases catecholamine output and reduces hyperdynamic state "that predisposes the myocardium to ischemia" and causes a mild bradycardia, which in turn facilitates the maintenance of a favorable oxygen supply-demand ratio (3). Intraoperative and postoperative hemodynamics stability may be the main mechanism through which the α_2-agonists might decrease preoperative ischemia (3). Clonidine can also preserve balance of sympathetic vs. parasympathetic nervous system that is necessary to maintain cardiac BRS and high frequency HRV and prevents development myocardial ischemia partially during early postoperative periods (7).

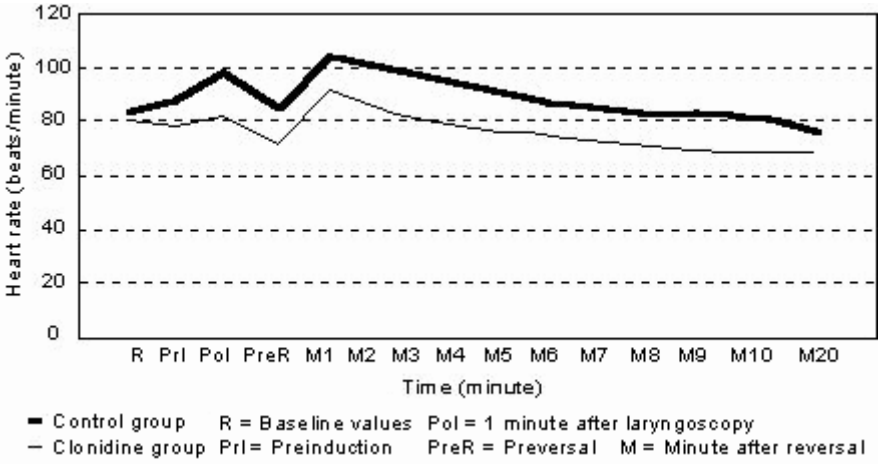
In a previous study, preventive effects of clonidine on heart rate changes after N-A injection has been supported (7). It seems that clonidine can decrease complications of HR changes secondary to N-A

Table 2: Comparison of postreversal heart rate and mean arterial blood pressure changes relative to the baseline in the clonidine and control groups.

Min. PoR		1	2	3	4	5	6	7	8	9	10	20
Control (n=40)	MAP	13 ± 16	14 ± 17	11 ± 18	9 ± 25	9 ± 17	7 ± 17	6 ± 17	5 ± 16	4 ± 17	4 ± 15	2 ± 16
	HR	20 ± 22	17 ± 23	13 ± 22	9 ± 20	5 ± 20	2 ± 21	-0.05 ± 21	-2 ± 21	-2 ± 21	-3 ± 21	-7 ± 16
Clonidine (n=40)	MAP	13 ± 19	12 ± 14	10 ± 13	6 ± 14	6 ± 13	4 ± 15	4 ± 14	4 ± 14	4 ± 15	3 ± 19	-2 ± 17
	HR	10 ± 20*	6 ± 20*	2 ± 19*	-1 ± 20*	-3 ± 20	-4 ± 19	-6 ± 18	-7 ± 17	-8 ± 16	-9 ± 16	-10 ± 14

- Values are mean ± SD
- HR = heart rate (beats/min)
- * P < 0.05 versus control group
- MAP = mean arterial blood pressure (mmHg)
- Min. PoR = minute postreversal

Figure 3: Comparison of heart rate changes from baseline to 20 minutes after neostigmine-atropine injection.Slope of HR changes in the clonidine and control groups are -2.09 and -2.72 respectively. Note HR changes 1 minute after reversal is more than 1 minute after laryngoscopy.



administration. The pattern of changes ocurring after oral clonidine on HR and MAP has not been elucidated clearly. Also, it was not clearly appreciated whether these changes were desirable (i.e., in the range of ± 10% of patients' baseline values) without producing significant hemodynamic instability or severe bradycardia or not. The purpose of the present study is to determine effects of oral clonidine premedication on HR and MAP changes after N-A administration under Halothane-N_2O-Atracurium anaesthesia and to measure the extent and clarify the pattern of these changes.

MATERIALS AND METHODS

Patients

After approval by our Investigational Review Board and obtaining informed consent from each patient, this double blind randomized clinical trial study was done on 80 adult patients, candidates for elective surgery of gynecology, orthopedics and laparotomy from May 1999 to April 2000 in Alzahra Medical Center. The patients' ages were between 18-65 years, and their weights were between 50-79 kg. All patients were in ASA physical status I or II. All patients randomized to two equal control and clonidine groups.

Exclusion criteria

The patients with history of diabetes mellitus, cardiovascular disorders, those with more than 15 seconds laryngoscopy, who needed intraoperative blood transfusion or any drug administration were excluded from the study.

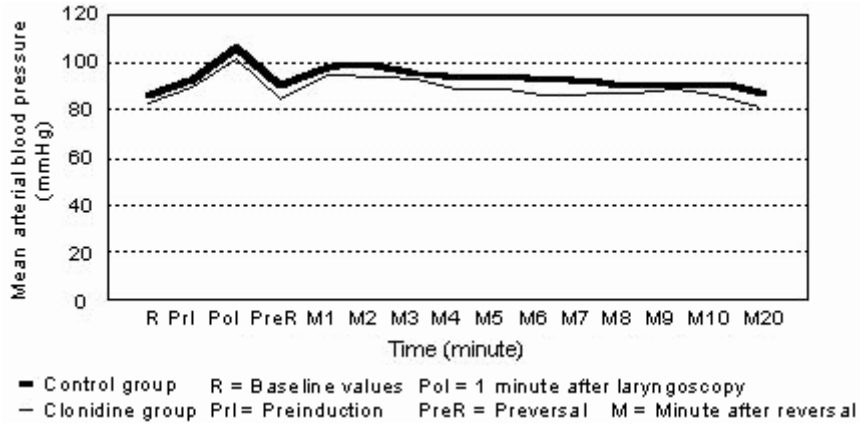
Study groups

The patients were randomly assigned to either the clonidine group (n=40), who received approximately 5 μg/kg clonidine (Catapres), or to the control group (n=40), who received starch alone orally 90 minutes before induction of general anaesthesia. Induction of anesthesia in all patients was induced with 5 mg/kg Thiopental and tracheal intubation was facilitated with 0.5 mg/kg Atracurium given intravenously. All patients were mechanically ventilated with 50% N_2O and 0.5-1% end tidal Halothane in oxygen during surgical procedures under Drager anesthetic machine. At the completion of surgery after reversal of patients' spontaneous ventilation and detecting three evoked muscle responses to TOF (Train-of-Four) stimulation (by INNERVATOR, Fisher and Paykel, Electronic. Ltd. Auckland, New Zealand), at the end-tidal CO_2 of <40 mmHg and SpO_2>95%, a mixture of atropine 0.02 mg/kg and neostigmine 0.05 mg/kg was administered slowly during 20 seconds and patients' trachea were extubated. In all patients, measurement of MAP and HR were made at 1 minute intervals for 10 minutes after N-A injection, and repeated after 10 minutes.

Statistical analysis

By using SPSS version 10 and Statistic version 4.5. Statistical software, the patients' characteristics were compared using unpaired student's t-test. MAP and HR responses to N-

Figure 4: Comparison of mean arterial blood pressure changes from baseline to 20 minutes after neostigmine-atripine injection.



A mixture over time were analyzed by factorial repeated measures analysis of variance (FRMAV) followed by Scheffe test probabilities as a *post hoc*, linear contrast and t-paired analysis (8). A p value < 0.05 was considered significant.

RESULTS

Based on our data, sex distribution in two groups was similar (each group contained 22 males and 18 females). There were no significant differences between the clonidine and control groups in terms of age (36±14 yr vs. 34±14 yr), weight (70±7 kg vs. 67±7 kg), height (168±10 cm vs. 170±9 cm), duration of surgery (105±29 min vs. 117±30 min), and $ETCO_2$ at extubation time (37±2 mmHg vs. 37±1 mmHg). The average dose of clonidine in the clonidine group was 4.9 μg/kg. There were no significant differences between groups in resting MAP (84±12 mmHg vs. 85±12 mmHg) and resting HR (80±12 beats/min vs. 84±18 beats/min).

Compared with the control group, absolute HR values in the clonidine group were significantly less between 1 to 10 minutes and at the 20th minute after injection (Figure 1). In the clonidine group, absolute MAP values were less than the control group but it was not significant (Table 1). In addition, increase in HR from baseline values of the clonidine group was significantly less than those of the control group 1-4 minutes after injection (Table 2).

Also, in the clonidine group, variability of HR values after injection were about ±10% of baseline values while they were about ±15-30% in the control group (Figure 2). On the other hand by using FRMAV followed by Scheffe test probabilities as a *post hoc*, there was significant difference in absolute HR changes after N-A between two groups ($p<0.01$), but absolute MAP changes were similar in two groups and there were no significant statistical differences between them.

By using linear contrast test, it was noticeable that the pattern of HR and MAP changes since resting until the 20th minute after N-A injection were linear in both groups, but there was no significant difference between their linearity (Figures 3 and 4).

Slope of postreversal HR changes in the clonidine and control groups was - 2.09 and -2.72 and constant coefficient of HR changes was 91.72 and 104.83 respectively. According to above data, we can obtain equations number 1 and 2 as below:

Equation no 1

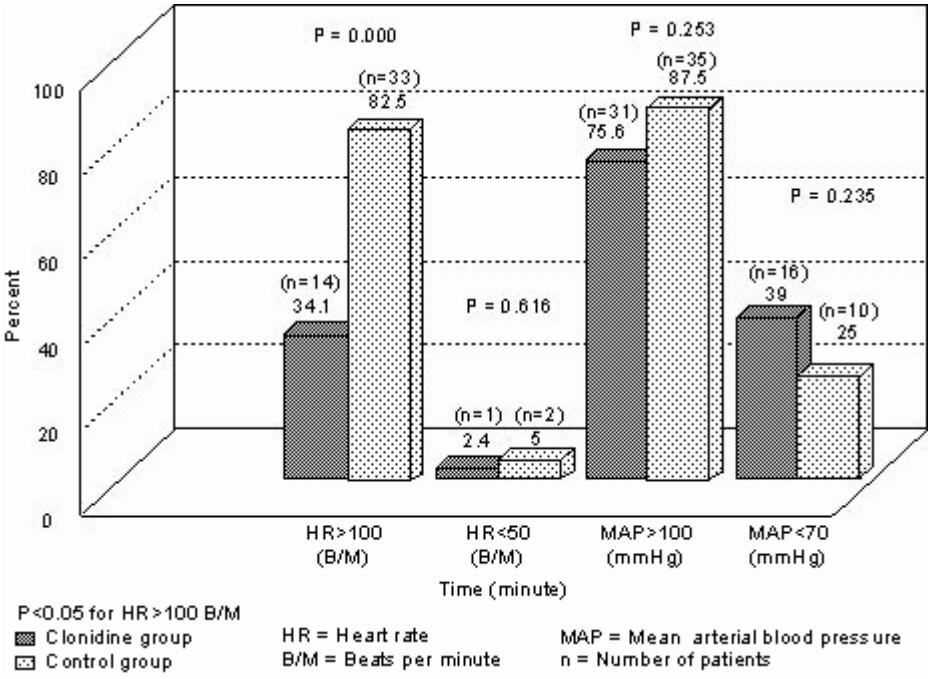
$y = -2.09x + 91.72$ in clonidine group

Equation no 2

$y = -2.72x + 104.83$ in control group

Noting Figure 3, it was also clear that 1 minute postreversal HR changes after N-A injection was more than 1 minute postlaryngoscopy, but it was not significant ($p>0.99$).

Figure 5: Frequency distribution percentage of tachycardia, bradycardia, hypotension and hypertension in the clonidine and control groups.



As shown in Figure 5, there was significant difference between frequencies of tachycardia (HR>100 beats/minute) in two groups by Chi-Square Tests (P=0.000). There was no significant difference between frequencies of severe bradycardia (HR<50 beats/minute), hypotension (MAP<70 mmHg) or hypertension (MAP>140 mmHg) in two groups. Also there was no patient in either group who developed any arrhythmias during the study period.

DISCUSSION

In one study before, effect of oral clonidine premedication on prevention of cardiovascular adverse effects after N-A injection had been studied (7). The purpose of the present study is confirmation of oral clonidine premedication effect on HR and MAP changes after N-A injection and evaluation of pattern and desirability of these variability. This study showed that 5 μg/kg oral clonidine 1.5 hours before induction of anesthesia attenuated initial increases, but did not enhance subsequent decreases in HR with minimal effects on MAP after N-A injection.

Also, our data showed that HR changes after N-A administration were about ±10% of baseline values in the clonidine group. Compared with the control group, total HR changes from baseline to the 20th minute after N-A were significantly less in the clonidine group while there was no such significant difference between MAP changes in two groups. In the clonidine group, slope of HR changes 1 to 10 minutes after N-A injection was less than the control group. Frequency of tachycardia was significantly less in the clonidine group compared with the control group.

Regarding the more rapid onset of hemodynamic changes after atropine injection comparing to neostigmine, it is concluded that initial increase in HR after N-A injection was due to atropine, and due to lower changes in clonidine group, it is deduced that either sympathetic nervous activity in the clonidine group was still partially depressed with comparable parasympa-

thetic activity between groups, or that preoperative clonidine preserve basal parasympathetic nervous activity at the time the study drugs were injected. Alternatively, a total abolition of parasympathetic activity by atropine may have been prevented by clonidine; because of baseline hemodynamic variables were comparable between the groups, suggesting that the balance of baseline sympathetic versus parasympathetic nervous system activities were also similar (9,2).

Our data showed that clonidine did not enhance subsequent reduction in HR, which is regarded primarily as the effect of intravenous neostigmine. Also, clonidine caused significant decrease in frequency of tachycardia in study group without producing severe bradycardia, hypotension or hypertension. Considering preservation of HR changes about ±10% of the baseline values after N-A injection, it seems that clonidine preserves HR component of hemodynamic variability about desired level by balancing sympathetic to parasympathetic tone in healthy adult patients (10).

In the study of Kimura *et. al.* (7), on 50 patients under general anaesthesia with Isoflurane-N_2O-Vecuronium, postreversal HR changes after N-A injection were significantly less between 1-5 minutes and between 7-9 minutes after injection while in our study on 80 patients under Halothane- N_2O-Atracurium anaesthesia, it was significant between 1 to 10 minutes and at the 20th minute after reversal. In the study of Kimura *et. al.*, there was no point of view on the pattern of HR and MAP changes after reversal and there was no quantitative measurement of these changes compared to the baseline values. Also it was not clear that postreversal HR and MAP changes were desirable (i.e., change between ±10% of the baseline values) or not. In our study, pattern of HR and MAP changes was considered (i.e., it was linear) and desirability of these changes was described.

Our study also showed that HR variability 1 minute after reversal was more than 1 minute after laryngoscopy. It must be pointed out that the latter has not been studied or considered elsewhere before in literature. However, it emphasizes the importance of preventive measures to attenuate these undesirable changes especially in high-risk patients, but needs confirmation.

Atropine at a dose of 0.02 mg/kg, which is similar to the dose known to produce maximum inhibition of vagal control of sinoatrial node (11), is recommended in clinical anesthesia when combined with neostigmine, because smaller doses of atropine produces unacceptable decrease in HR, whereas larger doses are associated with a greater incidence of dysrrythmia (12). It is also recommended that another study with different doses of oral clonidine to be conducted. Also we suggested studying not only effects of oral clonidine premedication on high-risk patients with history or risks of coronary artery disease and hypertension, but also on HR changes during intraoperative period. At last, it is necessary to design another study to determine that, “Is stress of reversal by N-A injection more than that of laryngoscopy?”

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REFERENCES

1. Scott RA and Belmont MA : Muscle relaxants and the cardiovascular system. Kaplan Jo Cardiac Anesthesia. Philadelphia, WB Saunders, pp 552-553, 1993.

2. Van Vlymen JM and Parlow JI : The effects of reversal of neuromuscular blockade on autonomic control in the preoperative period. Anesth Analg, 84:148-154, 1997.

3. Peden CA and Prys-Robert CE : The a2-adrenoceptor agonist and anesthesia. Prys-Robert CE and Brown Bu International Practice of Anesthesia. London, Butterworth Heinemann, p 1/19/10-1/19/12, 1996.

4. Savarese, Miller, Lien and Caldwell : Pharmacology of Muscle Relaxants and their Antagonists. Miller RD. Anesthesia, New York, Churchill Livingston, p 2154, 1994.

5. Collins VI : Reversal of relaxation: Antagonists to relaxant drugs. Collins VI. Pennsylvania, p 1028-1031, 1993.

6. Bartkowski RI and Horrow JA : Complications associated with muscle relaxants. Ed by NI Gravenstein, RO Kirbyl. In: Complications in Anesthesiology. Philadelphia, Lippincott-Raven publishers, p 667-669, 1996.

7. Kimura-T, Tanaka-M and Nishikawa-T : Effects of oral clonidine on heart rate changes after Neostigmine- Atropine administration. Anesthesiology, 88:1507-1510, 1998.8. Zar JH : Biostatistical analysis. Printed Hall International, pp 161-250, 1999.

9. Robinson BF, Epstein SE, Beiser D and Braunwald E : Control of heart rate by the autonomic nervous system. Circ Res, 19:400-411, 1966.

10. Ghingnone M, Noe C, Calvillo O and Quinitin L : Anesthesia for ophthalmic surgery in the elderly. The effect of clonidine on intraocular pressure, preoperative hemodynamics, and anesthetic requirement. Anesthesiology, 68:707-716, 1988.

11. Chamberlain DA, Turner P and Sueddon JM : Effects of atropine on heart rate in healthy man. Lancet, 2:12-15, 1967.

12. Mirakhur RK, Dundee JW, Jones CJ, Coppel DL and Clarke RS : Reversal of neuromuscular blockade: Dose determination studies with atropine and Glycopyrrolate given before or in a mixture with neostigmine. Anesth Analg, 60:557-562, 1981.

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