J Anesth (2009) 23:483–488
DOI 10.1007/s00540-009-0805-9

Journal of
Anesthesia

Effects of landiolol, a short-acting beta-1 blocker, on hemodynamic variables during emergence from anesthesia and tracheal extubation in elderly patients with and without hypertension

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Abstract
Purpose. Tracheal extubation and emergence procedures induce abrupt changes in hemodynamics and humoral responses. We conducted a prospective randomized study to examine the effects of the short-acting beta-1 blocker, landiolol, on hemodynamics during emergence from anesthesia in elderly patients with and without hypertension.
Methods. Thirty-one hypertensive and 32 normotensive elderly patients were randomly divided into two groups: a control (placebo group) and a landiolol infusion group. Landiolol was dissolved in 20 ml of saline and administered as an infusion at the rate of 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min and then decreased to 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$ until extubation. Control patients received an equal volume of saline. Heart rate and blood pressure were recorded every minute from immediately before the administration of landiolol up to the discontinuation of landiolol, and every 5 min from the discontinuation of landiolol to 30 min after termination of the infusion.
Results. Systolic blood pressure in the control group patients with hypertension increased during anesthesia emergence and tracheal extubation, as did the heart rate. Landiolol infusion in the elderly patients with hypertension partially prevented the increase in systolic blood pressure and completely prevented the increase in heart rate associated with emergence from anesthesia. Landiolol infusion in the elderly patients without hypertension brought about a decrease in heart rate during emergence and tracheal extubation.
Conclusion. This study indicates that the use of a landiolol infusion for preventing hemodynamic instability in elderly patients during the emergence period would be dependent on the presence or absence of hypertension in these patients.

Key words Emergence period · Beta-blocker · Landiolol · Heart rate

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Received: January 8, 2009 / Accepted: June 4, 2009

Introduction

It is well known that tracheal extubation and emergence from anesthesia induce abrupt changes in hemodynamics and humoral responses [1]. Many reports have documented that tracheal extubation causes transient increases in blood pressure and heart rate (HR), lasting from 5 to 15 min [1–3]. These hemodynamic changes during emergence from anesthesia may cause dangerous increases in myocardial oxygen demand in patients with coronary artery disease and in patients who have undergone neurosurgical procedures [2,3].

Several pharmacological agents have been evaluated to attenuate the physiological changes associated with tracheal extubation and the emergence period [1,4–6]. Of these agents, beta-blockers, such as labetalol, esmolol, and landiolol, are some of the most effective drugs for preventing these physiological changes. In contrast to esmolol [2–6,7–9], there have been very few reports regarding the effects of landiolol on the hemodynamic changes associated with emergence from anesthesia and extubation [10–13].

Prys Roberts et al. [14] reported that in both treated and untreated hypertensive patients, emergence from anesthesia followed by tracheal extubation was associated with significant increases in HR and arterial pressure compared to normotensive patients. Thus, it is reasonable to expect that hypertensive patients may exhibit an exaggerated hypertensive response to awakening and tracheal extubation compared to that seen in normotensive patients.

For the past 20 to 30 years, the number of elderly patients undergoing surgery has been steadily rising throughout the world [15]. It is important for anesthesiologists to manage hemodynamic stability during anesthetic emergence and tracheal extubation in elderly patients. We hypothesized that the short-acting beta-1 blocker, landiolol, would have differential effects on hemodynamics during emergence from anesthesia and

tracheal extubation in elderly patients with and without hypertension.

The purpose of this study was to examine the effects of the short-acting beta-1 blocker, landiolol, on hemodynamics during the emergence period in elderly patients with and without hypertension.

Patients and methods

This study was approved by the Ethics Committee of our institute, and written informed consent was obtained from all patients. Elderly patients were defined as those above 70 years of age. Patients who were American Society of Anesthesiology (ASA) physical status 3, 4, or 5 or had an atrioventricular conduction block greater than first degree or a history of drug allergy were excluded from the study. Additional exclusion criteria were: history of asthma, bronchospasm, chronic obstructive pulmonary disease, coronary artery disease, HR less than 50 beats·min^{-1}, and systolic blood pressure less than 80 mmHg 1 min before the administration of landiolol.

Control patients were defined as normotensive individuals who had never been diagnosed as being hypertensive on medical examinations. Patients with hypertension were defined as those taking oral antihypertensive medication at the first hospital arrival. In addition, all hypertensive patients selected were controlled hypertensives with normal blood pressure levels (systolic blood pressure below 139 mmHg), as a result of treatment with antihypertensive drugs, at the time of hospital admission. Patients with uncontrolled hypertension were excluded from this study due to the possibility that these patients would require additional antihypertensive drugs during the emergence and extubation periods, which could possibly confound the results. Patients with uncontrolled hypertension were defined as those with elevated blood pressure levels (systolic blood pressure above 160 mmHg) despite treatment with antihypertensive drugs at the time of hospital admission [16]. None of the hypertensive patients were receiving beta-blockers.

For all the hypertensive patients, antihypertensive drug therapy was administered on the morning of surgery.

Study protocol

Thirty-one hypertensive and 32 normotensive elderly patients scheduled for orthopedic or gynecological surgery were randomly divided into two groups: a control (placebo group) and a landiolol infusion group, group selection being determined by a random number table.

A three-lead electrocardiography monitor was attached to all patients (Nihon Koden, Tokyo, Japan). Anesthesia was induced with 2 mg·kg^{-1} of propofol and 0.6 mg·kg^{-1} of rocuronium, followed by endotracheal intubation. Muscular relaxation was achieved by intermittent administration of rocuronium. In all the patients, the lungs were ventilated with 40% oxygen and 60 % N2O with continuous monitoring of end-tidal carbon dioxide (PetCO2; Nihon Koden,). Anesthesia was maintained with remifentanyl, 0.2–0.5 μg·kg^{-1}·min^{-1}, and 0.5%–1.0% sevoflurane in 40% oxygen and 60% N2O.

Bispectral index monitoring (A-2000; ASPECT Medical Systems, Natic, MA, USA) was used to assess the anesthetic depth in each group. Target BIS levels were from 45 to 50. After the induction of anesthesia, the administration of anesthetic agents, remifentanil, and sevoflurane, was adjusted to maintain BIS levels from 45 to 50 in all patients during the study period.

Immediately after the end of the surgery, administration of all anesthetics, including sedative agents, was discontinued. All patients were then ventilated with 100% oxygen for emergence from anesthesia, and depending on the group, either a landiolol infusion or normal saline infusion was started. All persons present during the study were blinded to the identity of the infusion being administered (drugs were given using foil-covered cylinders and lines). One vial of landiolol (50 mg) was dissolved in 20 ml of saline.

In the landiolol-group patients, the landiolol infusion was administered at the rate of 0.125 mg·kg^{-1}·min^{-1} for 1 min and then decreased to 0.04 mg·kg^{-1}·min^{-1} until extubation. Control group patients received an equivalent volume of normal saline. Details of the study protocol are shown in Fig. 1. When spontaneous breathing was observed after surgery, 0.03–0.04 mg·kg^{-1} of neostigmine and 0.01–0.02 mg·kg^{-1} of atropine sulfate were given over a 1-min period. After the patients could breathe spontaneously and open their eyes on command, extubation was performed.

Heart rate and blood pressure were recorded every minute from before the administration of landiolol/saline infusion up to discontinuation of the infusion, and every 5 min subsequently, to 30 min after termination of the infusion.

All patients received patient-controlled analgesia with an intravenous infusion of fentanyl from the end of the surgery. Twenty micrograms of fentanyl per hour was given to each patient, and a rescue dose of 10 μg of fentanyl was prepared when necessary.

Statistical analysis

Data were analyzed at a later time by an individual who was also blinded to the treatment regimens. Before the

start of this study protocol, we calculated sample sizes. Based on a previous study [13], we hypothesized that HR in the landiolol group would decrease by 15 beats·min^{-1} compared with that in control patients. We determined that 15 members in each group would be required to provide 80% power to detect a 20% difference between the landiolol and control groups.

All data are expressed as means ± SD. Following the confirmation of equal variance among the groups by the Bartlett test, changes in mean values of HR, systolic blood pressure, and mean blood pressure (baseline and between groups) were compared using one-way factorial measure or two-way repeated-measures analysis of variance (ANOVA). When the *F* value was significant, the Bonferroni method was used for multiple comparisons. Demographic data of the four groups were analyzed by one-way repeated-measures ANOVA. All calculations were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA) and StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

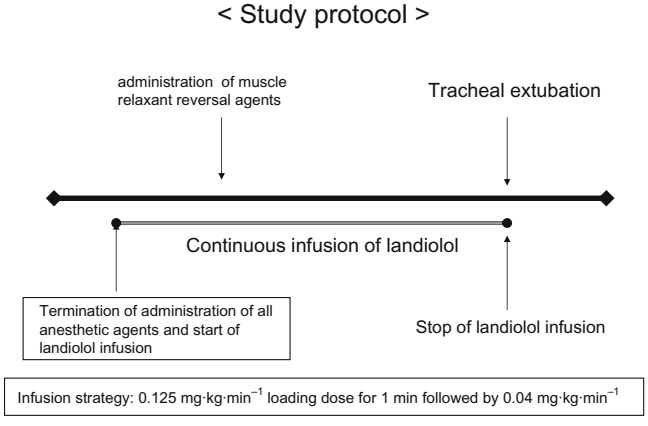

Fig. 1. Schematic diagram of the study protocol

Results

Table 1 shows the demographic data of the four groups. There were no significant differences in age, height, weight, anesthetic time, surgical time, blood loss, urine output, reversal dosage of muscle relaxant, or opiate dosage during anesthesia between the four groups. In addition, landiolol infusion time, defined as the duration from the start of administration of landiolol to the discontinuation of landiolol, was almost identical between groups.

Figures 2 and 3 show the time courses of changes in systolic blood pressure and HR in the four groups. Systolic blood pressure in the hypertensive control group increased during emergence and tracheal extubation. Landiolol infusion partially prevented the increase in systolic blood pressure associated with emergence from anesthesia in the elderly patients with hypertension. Systolic blood pressure in the elderly normotensive control-group patients increased slightly during emergence and tracheal extubation. No increase in systolic blood pressure in the elderly patients without hypertension was observed in the landiolol group throughout the study period.

Heart rate in the control-group patients with hypertension increased during emergence and tracheal extubation. Landiolol infusion in the elderly patients with hypertension prevented this increase in HR. Heart rate in the control-group patients without hypertension

Table 1. Demographic data of the four groups

	No-hypertension group		Hypertension group		
	Control	Landiolol group	Control	Landiolol group	*P* value
Number of patients	16	16	15	16	
Age (years)	76 ± 5	73 ± 3	75 ± 4	74 ± 4	0.17
Height (cm)	154 ± 6	155 ± 9	155 ± 8	153 ± 7	0.91
Weight (kg)	53 ± 7	55 ± 12	55 ± 8	54 ± 11	0.92
Anesthetic time (min)	223 ± 89	207 ± 101	246 ± 109	218 ± 123	0.77
Operation time (min)	162 ± 82	154 ± 106	185 ± 109	160 ± 113	0.84
Blood loss (ml)	213 ± 182	360 ± 703	322 ± 543	422 ± 590	0.73
Urine output (ml)	273 ± 133	230 ± 207	309 ± 293	345 ± 348	0.63
Landiolol infusion time (min)	21 ± 3	22 ± 4	21 ± 3	21 ± 2	0.83
Reversal dosage					
Atropine sulfate (mg)	0.87 ± 0.22	0.90 ± 0.20	1.00 ± 0.01	0.93 ± 0.17	0.23
Neostigmine (mg)	1.6 ± 0.4	1.7 ± 0.4	1.8 ± 0.2	1.7 ± 0.3	0.34
Opiate dosage					
Remifentanil (mg)	1.7 ± 1.0	1.5 ± 0.8	1.7 ± 0.8	1.9 ± 1.5	0.67

Data are expressed as means ± SD
Landiolol infusion time was defined as the time interval from the start of administration of landiolol to the discontinuation of landiolol

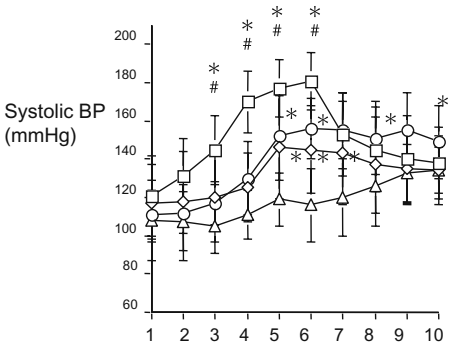

Fig. 2. Time course of changes in systolic blood pressure (*BP*) in the four groups. $^{*}P < 0.05$ compared with time point 1; $^{\#}P < 0.05$ compared with other groups. *Time point 1*, Pre-infusion; *2*, 1 min after the administration of landiolol; *3*, 2 min after the administration of landiolol; *4*, 5 min after the administration of landiolol; *5*, 10 min after the administration of landiolol; *6*, 15 min after the administration of landiolol; *7*, at the time of termination of landiolol; *8*, 5 min after termination of landiolol; *9*, 10 min after termination of landiolol; *10*, 15 min after termination of landiolol. *Squares*, hypertension (HT) control; *diamonds*, HT landiolol; *circles*, no HT control; *triangles*, no HT landiolol

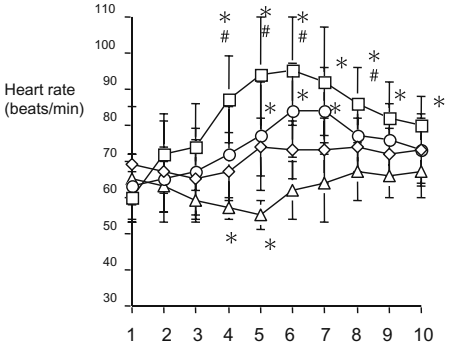

Fig. 3. Time course of changes in heart rate in the four groups. $^{*}P < 0.05$ compared with time point 1; $^{\#}P < 0.05$ compared with other groups. *Time point 1*, pre-infusion; *2*, 1 min after the administration of landiolol; *3*, 2 min after the administration of landiolol; *4*, 5 min after the administration of landiolol; *5*, 10 min after the administration of landiolol; *6*, 15 min after the administration of landiolol; *7*, at the time of termination of landiolol; *8*, 5 min after termination of landiolol; *9*, 10 min after termination of landiolol; *10*, 15 min after termination of landiolol. *Symbols*, as in Fig. 2

increased during emergence and tracheal extubation, while landiolol infusion in the normotensive patients decreased the HR during emergence and tracheal extubation. The HR in normotensive patients with landiolol was greatly decreased at 10 min after the administration of landiolol infusion (from 44 to 68 beats·min^{-1}, three patients had an HR below 50 beats·min^{-1} at this point). None of the patients in the other three groups had an HR below 50 beats·min^{-1} at any time point.

Discussion

The present study shows that the administration of landiolol can prevent the increase in HR in elderly patients with hypertension during emergence from anesthesia. However, the administration of landiolol decreases the HR in elderly patients without hypertension during emergence from anesthesia.

Many reports have documented that transient hemodynamic changes are induced during tracheal extubation and emergence from anesthesia, and these changes may sometimes cause dangerous increases in myocardial oxygen demand in patients with coronary artery disease [1, 17, 18]. Coriat et al. [17] showed that patients with coronary artery disease experienced significant decreases in ejection fraction (from 55 ± 7% to 45 ± 7%) after extubation. Wellwood et al. [18] reported that patients with a cardiac index of less than 3.0 l·min^{-1} demonstrated an ischemic response to the stress of postoperative tracheal extubation after myocardial revascularization. These reports imply that it is important to attenuate the physiological changes associated with tracheal extubation and emergence from anesthesia.

Among the several pharmacological agents available, beta-blockers are some of the most effective drugs for preventing the hemodynamic changes associated with recovery from anesthesia and surgery [1]. Dyson et al. [9] examined the effects of three doses of esmolol (1.0, 1.5, and 2.0 mg·kg^{-1}) given as a bolus 2 min after the reversal of neuromuscular blockade with isoflurane anesthesia, and found that all doses of esmolol attenuated increases in HR, although 1.0 mg·kg^{-1} was insufficient to control increases in blood pressure and 2.0 mg·kg^{-1} of esmolol produced significant decreases in systolic blood pressure. Kurian et al. [2] examined the effects of an infusion of esmolol on the incidence of myocardial ischemia during tracheal extubation following coronary artery surgery, and showed that, although the use of esmolol reduced the incidence of myocardial ischemia (12/37 in the control group, 3/31 in the esmolol group; $P = 0.05$), adverse effects, such as bradycardia or hypotension, were often observed in the esmolol group as compared to control patients. They decided to terminate their study early because of these adverse events and difficulties with patient recruitment.

In contrast to esmolol, few studies have examined the effects of landiolol on hemodynamics during extubation and emergence from anesthesia and surgery. Nonaka et al. [10] examined the effects of the administration of 0.125 mg·kg^{-1}·min^{-1} of landiolol for 1 min on hemodynamic changes after the injection of neostigmine-atropine, and observed that the maximum increase in HR was 29.6 ± 12.3 beats·min^{-1} in the control group, whereas it was 14.1 ± 11.9 beats·min^{-1} in the landiolol group. Minamizono et al. [11] and Ohata et al. [12] observed

the same results. Shirasaka et al. [13] examined the effects of the continuous administration of different doses of landiolol on the cardiovascular response during tracheal extubation, and found that landiolol could prevent increases in HR and blood pressure in patients without hypertension. The present study is the first of its kind to compare the effects of landiolol on hemodynamic changes in elderly patients with and without hypertension during the emergence period. Landiolol exhibits a predominant chronotropic effect, rather than an inotropic effect, and thus causes neither excessive hypotension nor cardiac decompression [7]. The findings of our study concur with previous reports regarding the attenuation only of increases in HR by landiolol.

Reports by Prys Roberts et al. [14] and Stone et al. [19] imply that it is of special clinical importance to maintain hemodynamic stability in patients with hypertension during emergence from anesthesia. Sugiura et al. [20] showed that in hypertensive patients, 0.2 $mg \cdot kg^{-1}$ landiolol was necessary to suppress tachycardia after intubation, whereas 0.1 $mg \cdot kg^{-1}$ was effective in normotensive patients. This demonstrates that a larger dose of landiolol is required to prevent hemodynamic changes in hypertensive patients compared with normotensive patients. In contrast, Shirasaka et al. [13] showed that landiolol could prevent the increases in both HR and blood pressure in patients without hypertension, although a lower dose was required for preventing tachycardia as compared to preventing elevations in blood pressure in these patients. Slogoff and Keats [21] have shown that perioperative myocardial ischemia is significantly related to episodes of tachycardia, but not to episodes of hypertension. It thus appears reasonable that it is of greater clinical importance to avoid tachycardia during emergence from anesthesia, rather than preventing hypertension.

We observed that the HR in only the normotensive patients fell below 50 $beats \cdot min^{-1}$. Although we did not measure cardiac output in our patients, elderly normotensive patients may be at risk of developing bradycardia-induced low cardiac output. Our study indicates that beta-blocker therapy during emergence from anesthesia should be used with caution in elderly nonhypertensive patients, due to the risk of severe bradycardia.

Study limitations

Different doses of muscle relaxant reversal agents may have different effects on hemodynamic variables [22,23], This confounding factor, however, may not have significantly affected our results, as no significant differences in doses of muscle relaxant reversal agents were observed between groups in this study.

In this study, we excluded patients with uncontrolled hypertension. It is, however, possible that more highly exacerbated hemodynamic changes may be observed in patients with uncontrolled hypertension.

In conclusion, the present study showed that, in elderly patients with hypertension, landiolol can prevent the increase in HR but not the increase in blood pressure during emergence from anesthesia. In contrast, in elderly patients without hypertension, landiolol decreases the HR during emergence from anesthesia.

References

1. Miller KA, Harkin CP, Bailey PL. Postoperative tracheal extubation. Anesth Analg. 1995;80:149–72.
2. Kurian SM, Evans R, Fernandes NO, Sherry KM. The effect of an infusion of esmolol on the incidence of myocardial ischemia during tracheal extubation following coronary artery surgery. Anaesthesia. 2001;56:1163–8.
3. Grillo P, Bruder N, Auquier P, Pellissier D, Gouin F. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. Anesth Analg. 2003;96: 1145–9.
4. Kovac A, Masiongale A. Comparison of nicardipine versus esmolol in attenuating the hemodynamic responses to anesthesia emergency and extubation. J Cardiothoracic Vasc Anesth. 1999; 16:145–9.
5. Dryden CM, Smith DM, McLintic AJ, Pace NA. The effect of preoperative beta-blocker therapy on cardiovascular responses to weaning from mechanical ventilation and extubation after coronary artery bypass grafting. J Cardiothorac Vasc Anesth. 1993;7: 547–50.
6. Muzzi DA, Black S, Losasso TJ, Cucchiara RF. Labetalol and esmolol in the control of hypertension after intracranial surgery. Anesth Analg. 1990;70:68–71
7. Mio Y. New ultra-short-acting beta-blockers: landiolol and esmolol—the effects on cardiovascular system. Masui. 2006;55: 841–8.
8. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. Can J Anaesth. 2001; 48:985–9.
9. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM. Esmolol attenuates cardiovascular responses to extubation. Anesth Analg. 1990;71:675–8.
10. Nonaka A, Suzuki S, Abe F. The effects of continuous infusion of landiolol on heart rate changes after neostigmine-atropine administration during recovery from general anesthesia. Masui. 2006;55:1459–62.
11. Minamizono T, Goyagi T, Nishikawa T. Effects of landiolol on hemodynamic changes during tracheal extubation (in Japanese). J Clin Anesth (Jpn). 2006;30:533–7
12. Ohata H, Ando T, Sudani T, Nagasaka Y, Fukuoka N, Dohi S. Effects of landiolol on hemodynamic changes during recovery from general anesthesia (in Japanese). J Clin Anesth (Jpn). 2004;24:579–85.
13. Shirasaka T, Iwasaki T, Hosokawa N, Komatsu M, Kasaba T, Takasaki M. Effects of landiolol on the cardiovascular response during tracheal extubation. J Anesth. 2008;22:322–5.
14. Prys-Roberts C, Meloche R, Poex P. Studies of anesthesia in relation to hypertension. I: cardiovascular responses of treated and untreated patients. Br J Anesth. 1971;43:122–37.
15. Muravchick S. Nervous system aging. In: McLeskey CH, editor. Geriatric anesthesiology. Baltimore: Williams & Wilkins; 1997. p. 29–41.

16. Kadoi Y, Saito S, Takahashi K. The comparative effects of sevoflurane vs isoflurane on cerebrovascular carbon dioxide reactivity in patients with hypertension. Acta Anaesthesiol Scand. 2007;51: 1382–7.
17. Coriat P, Mundler O, Bouseau D, Fauchet M, Rous AC, Echter E, Viars P. Response of left ventricular ejection fraction to recovery from general anesthesia: measurement by gated radionuclide angiography. Anesth Analg. 1986;65:593–600.
18. Wellwood M, Aylmer A, Teasdale S. Extubation and myocardial ischemia (abstract). Anesthesiology. 1984;61:A132.
19. Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Riner L. Risk of myocardial ischemia in treated and untreated hypertensive patients. Br J Anesth. 1988;61:675–9.
20. Sugiura S, Seki S, Hidaka K, Masuoka M, Tsuchida H. The hemodynamic effects of landiolol, an ultra-short-acting β1-selective blocker, on endotracheal intubation in patients with and without hypertension. Anesth Analg. 2007;104:124–9.
21. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology. 1985;62: 107–14.
22. Kimura T, Tanaka M, Nishikawa T. Comparison of heart rate changes after neostigmine-atropine administration during recovery from propofol-N2O and isoflurane-N2O anesthesia. J Anesth. 2002;16:23–7.
23. Naguib M, Gomaa M. Atropine-neostigmine mixture: a dose-response study. Can J Anaesth. 1989;36:412–7.