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Comparison of heart rate changes after neostigmine-atropine administration during recovery from propofol-N_2O and isoflurane-N_2O anesthesia

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Abstract

Purpose. Propofol augments the reduction of heart rate (HR) in combination with cholinergic agents and attenuates the HR response to atropine. We examined whether propofol anesthesia was associated with an increased incidence and extent of bradycardia after neostigmine-atropine administration compared with the effects of isoflurane anesthesia.

Methods. Thirty-six adult patients were randomly assigned to two groups ($n = 18$ each): the propofol group patients were anesthetized with propofol (5–10 mg·kg^{-1}·h^{-1})-N_2O-fentanyl, and the isoflurane group patients were anesthetized with isoflurane (0.5%–1.0%)-N_2O-fentanyl. When surgery was completed, anesthetics were discontinued, and then a mixture of neostigmine 0.05 mg·kg^{-1} and atropine 0.02 mg·kg^{-1} was injected intravenously over 20 s. Blood pressure (BP) and HR were measured noninvasively at 1-min intervals for 10 min.

Results. At the completion of the surgery, the average infusion rate of propofol was 6.2 ± 1.7 mg·kg^{-1}·h^{-1}, and the average inspired concentration of isoflurane was 0.73 ± 0.15%. Immediately before the neostigmine-atropine injections, HR and mean BP were similar in the two groups. The maximum increase in HR after the neostigmine-atropine injections was significantly less in the propofol group than in the isoflurane group (16 ± 9 and 34 ± 6 beats·min^{-1}, respectively, $P < 0.01$). The subsequent maximum decrease in HR was greater in the propofol group than in the isoflurane group (−9 ± 4 and −5 ± 4 beats·min^{-1}, respectively; $P < 0.01$). The incidence of bradycardia (HR < 50 beats·min^{-1}) after neostigmine-atropine injection was greater in the propofol group than in the isoflurane group (61% and 28%, respectively; $P < 0.01$).

Conclusion. We conclude that propofol anesthesia attenuates the initial increases in HR, enhances the subsequent decreases in HR, and increases the incidence of bradycardia after neostigmine-atropine injections compared with the effects of isoflurane anesthesia.

Key words Atropine · Neostigmine · Propofol · Isoflurane · Bradycardia

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Introduction

A neostigmine-atropine mixture may be used to antagonize nondepolarizing muscle relaxants. On the reversal of muscle relaxants when such drug combinations are used, heart rate (HR) changes are affected by the anesthetics administered to the patients [1–3], and moderate bradycardia has been reported to occur in some patients [1,3–5].

Propofol is reported to reduce parasympathetic tone to a lesser extent than sympathetic tone [6] and to cause bradyarrhythmia in combination with various drugs and other factors that could potentially stimulate the parasympathetic nervous system [7,8]. Attenuated HR responses to intravenous atropine have also been reported in patients anesthetized with propofol [9]. Therefore, propofol may attenuate the initial increases and augment the subsequent decreases in HR after intravenous injections of a neostigmine-atropine mixture. To the best of our knowledge, however, the effects of propofol-based anesthesia on HR changes after the administration of a neostigmine-atropine mixture have neither been examined, nor have they been compared with the changes that occur with other anesthetic techniques. Accordingly, this study was designed to test the hypothesis that the initial increase in HR is attenuated, whereas the subsequent decrease in HR is augmented, after a neostigmine-atropine injection during propofol anesthesia compared with the effects of isoflurane anesthesia. We also compared the incidence and degree of bradycardia with these two anesthetic techniques.

Subjects and methods

The study protocol was approved by our local ethics committee, and informed consent was obtained from each patient. Thirty-six adult patients, American Society of Anesthesiologists (ASA) I or II, scheduled

for elective surgery under general anesthesia were studied. The type of surgery was otolaryngeal, orthopedic, or minor superficial surgery. Patients with a history of cardiovascular disorders, diabetes mellitus, disorders known to affect autonomic function, and those taking medications known to affect cardiovascular function or whose resting HR was <50 beats·min^{-1} were excluded. All patients received oral famotidine (an H_2-blocker) 20 mg 90 min before the induction of general anesthesia.

On the patient's arrival in the operating room, a 20-gauge intravenous cannula was inserted, and acetated Ringer's solution was administered at a rate of approximately 5 ml·kg^{-1}·h^{-1} throughout the study period. Standard lead II electrocardiography (ECG; NEC San-ei Instrument, Tokyo, Japan) was performed and an automated blood pressure (BP) cuff (BP-308ET; Nippon Colin, Tokyo, Japan) was applied at the contralateral arm. HR, determined from the average R-R intervals every 4 s from the ECG monitor, and mean BP (MBP) were electronically calculated.

The patients were randomly assigned to either the isoflurane or propofol group ($n = 18$ each). Random allocations to these groups were made according to a computer-generated number table. After the measurement of preinduction BP and HR, general anesthesia was induced with intravenous thiopental 5 mg·kg^{-1} plus fentanyl 2 μg·kg^{-1} in the isoflurane group, or with intravenous propofol 2 mg·kg^{-1} plus fentanyl 2 μg·kg^{-1} in the propofol group. Tracheal intubation was facilitated with intravenous vecuronium 0.1 mg·kg^{-1}. Then, the patients' lungs were mechanically ventilated to maintain end-tidal CO_2 tension at 35–45 mmHg with a fresh gas flow of 6 l·min^{-1} throughout the study period. Anesthesia was maintained with 0.5%–1.0% inspired concentration of isoflurane and 70% nitrous oxide in oxygen in the isoflurane group, or with continuous infusion of propofol (5–10 mg·kg^{-1}·h^{-1}) and 70% nitrous oxide in oxygen in the propofol group. The inspired isoflurane concentration and the infusion rate of propofol were adjusted to maintain systolic BP and HR within the range of ±20% of the preinduction values. All patients received fentanyl 0.5 μg·kg^{-1} intravenously at 30-min intervals from the induction of anesthesia to the end of the surgery. No additional vecuronium or other anesthetics was used.

At the completion of the surgery, all anesthetic agents were discontinued, while mechanical ventilation was continued with 100% oxygen. Immediately after the discontinuance of anesthetic agents, BP and HR were measured (preinjection BP and HR) and then a mixture of neostigmine 0.05 mg·kg^{-1} and atropine 0.02 mg·kg^{-1} was injected intravenously over 20 s. Measurements of BP and HR were made at 1-min intervals for 10 min after the neostigmine-atropine injections, and the highest HR value measured during this period was defined as the maximum HR in each patient. No stimulus, including intratracheal or oral suction, was given to the patients during this 10-min measurement period. Bradycardia was defined as HR <50 beats·min^{-1} after neostigmine-atropine injection. If HR decreased to <45 beats·min^{-1}, additional atropine 0.01 mg·kg^{-1} was administered repeatedly until a stable HR of >45 beats·min^{-1} was obtained. Patients who received additional atropine administration were excluded from the subsequent analysis. After the completion of the 10-min measurement period, verbal commands to open their eyes were given to the patients at 1-min intervals. The patients' tracheae were extubated after we confirmed that there were adequate responses to verbal commands, and that there was spontaneous respiration with end-tidal CO_2 tension of <45 mmHg.

For power analysis, we used data from our pilot study that examined HR changes after intravenous injections of the neostigmine-atropine mixture, which revealed that at least 16 patients in each group would provide a significance (α) of 0.05 and a power (β) >0.9 for the detection of an approximately 30% difference in maximum HR changes between two groups [10]. All data values are expressed as mean ± SD. Comparisons of patient characteristics and BP and HR between the groups were made using the unpaired Student's *t*-test. Testing for differences in incidences between the groups was accomplished by χ^2 analysis or Fisher's exact test as appropriate. BP and HR responses to intravenous injections of the neostigmine-atropine mixture over time were analyzed by repeated-measures analysis of variance (ANOVA), followed by Fisher's protected least-significance method as a post-hoc test. Correlations between preinjection HR and minimum HR values after the neostigmine-atropine injections were analyzed by Pearson's correlation coefficient. A P value of <0.05 was considered statistically significant.

Results

There were no significant differences between the propofol and isoflurane groups in terms of age (44 ± 4 and 49 ± 18 years), height (162 ± 9 and 159 ± 9 cm), weight (58 ± 10 and 58 ± 13 kg), male/female ratio (8:10 and 12:6), anesthesia time (120 ± 52 and 141 ± 77 min), surgery time (89 ± 49 and 112 ± 71 min), average fentanyl dose (3.4 ± 0.8 and 3.6 ± 1.1 μg·kg^{-1}), pre-induction MBP (88 ± 15 and 91 ± 12 mmHg), and preinduction HR (67 ± 11 and 69 ± 13 beats·min^{-1}). Average durations from discontinuance of all anesthetics until eye opening (15 ± 7 and 12 ± 2 min) and tracheal extubation (18 ± 7 and 15 ± 2 min) were also similar in the two groups. The average infusion rates of propofol during the entire course of anesthesia and at the completion of

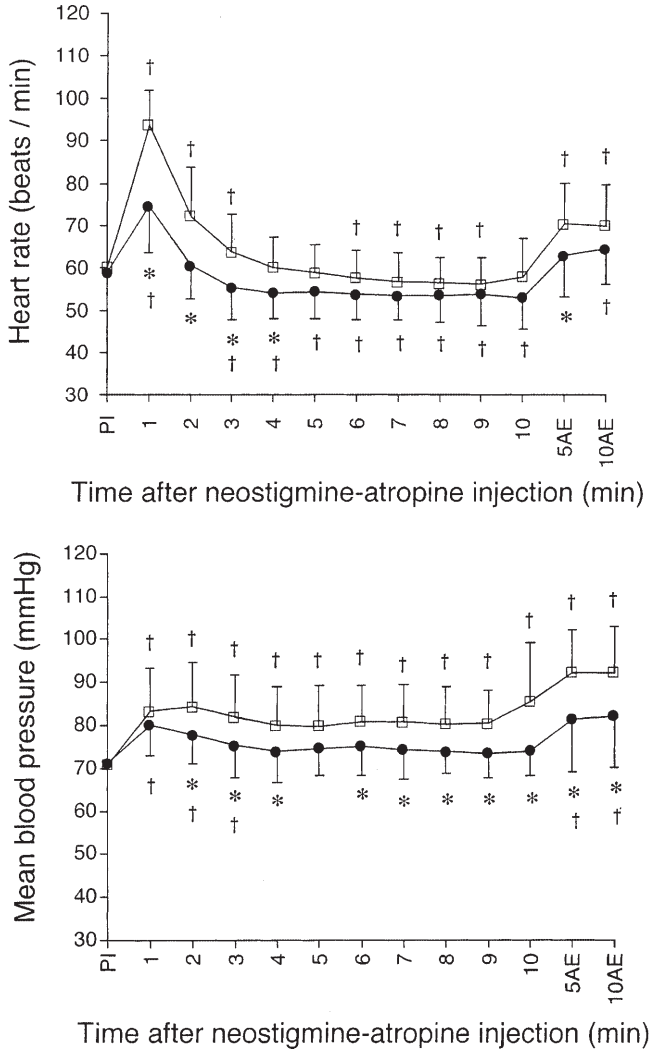

Fig. 1. **a** Heart rate and **b** mean blood pressure changes after neostigmine 0.05 mg·kg^{-1} and atropine 0.02 mg·kg^{-1} mixture injections. Data values are means ±SD. *PI*, Preinjection; *5AE* and *10AE*, 5 and 10 min, respectively, after tracheal extubation. *$P < 0.05$ *vs* isoflurane group; †$P < 0.05$ *vs* preinjection values. *Open squares*, Isoflurane group; *closed circles*, propofol group

the surgery were 6.6 ± 1.3 and 6.2 ± 1.7 mg·kg^{-1}·h^{-1}, respectively. The average inspired concentration of isoflurane at the completion of the surgery was 0.73% ± 0.15%.

Preinjection (i.e., immediately before the neostigmine-atropine injection) HR was similar in the two groups. Injections of the neostigmine-atropine mixture produced a similar hemodynamic pattern in both groups of initial increases and then subsequent decreases in HR (Fig. 1a). However, compared with the values in the isoflurane group, absolute HR values and changes in HR from preinjection values were less in the propofol group between 1 and 4 min after injections, and at 5 min after tracheal extubation (repeated-measures ANOVA; $P < 0.05$). After the neostigmine-atropine injection, the mean maximum increase in HR from preinjection values was less in the propofol group than in the isoflurane group (16 ± 9 and 34 ± 6 beats·min^{-1}, respectively; $P < 0.0001$). Furthermore, the mean maximum decrease from preinjection values in HR was greater in the propofol group than in the isoflurane group (−9 ± 4 and −5 ± 4 beats·min^{-1}, respectively; $P < 0.01$). The time until the maximum HR was attained after the neostigmine-atropine injection was 1 min in all patients in both groups, while the times until the minimum HR was attained were similar in the propofol and isoflurane groups (7.5 ± 2.6 and 8.6 ± 1.7 min, respectively; $P = 0.12$). Absolute MBP values were lower in the propofol group than in the isoflurane group from 2 min after the neostigmine-atropine injection to 10 min after tracheal extubation, except at 5 min (Fig. 1b).

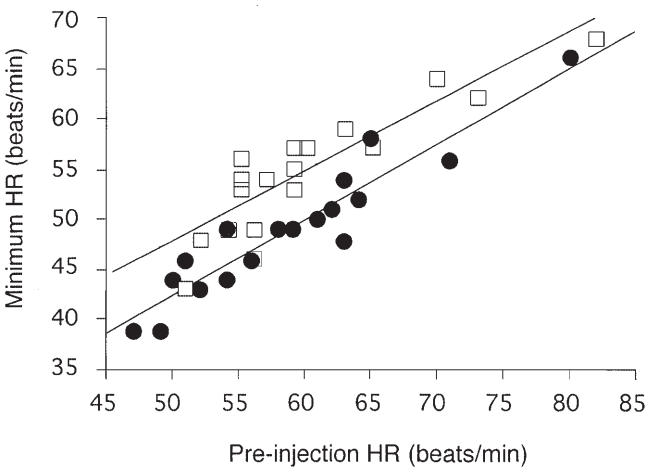

Fig. 2. Correlations of the preinjection heart rate (*HR*) with ensuing minimum HR after neostigmine 0.05 mg·kg^{-1} and atropine 0.02 mg·kg^{-1} mixture injections, with lines of best fit by simple linear regression analysis. Propofol group ($n = 18$; *closed circles*): $y = 0.65x + 11.35$ ($r^2 = 0.87$; $P < 0.05$). Isoflurane group ($n = 18$; *open squares*): $y = 0.69x + 13.10$ ($r^2 = 0.79$; $P < 0.05$)

Eleven of the 18 patients (61%) in the propofol group and 5 of the 18 (28%) in the isoflurane group developed bradycardia, defined as HR <50 beats·min^{-1}, after the neostigmine-atropine injection ($P < 0.01$). Additional intravenous atropine 0.01 mg·kg^{-1} was required in 5 of the 18 patients (28%) in the propofol group, and in only 1 of the 18 (6%) patients in the isoflurane group to obtain HR values >45 beats·min^{-1}.

There were significant correlations between the preinjection HR and the minimum HR values after the neostigmine-atropine injections in both groups (Fig. 2). The regression line in the propofol group was shifted toward the right compared with that in the isoflurane group. In the propofol group, all 10 patients (100%)

whose preinjection HR values were <60 beats·min^{-1} eventually developed a minimum HR of <50 beats·min^{-1} after the neostigmine-atropine injections, while in the isoflurane group, 5 of 12 patients (42%) whose preinjection HR values were <60 beats·min^{-1} developed an ensuing minimum HR of <50 beats·min^{-1} ($P < 0.01$).

No patients showed dysrhythmias other than bradyarrhythmia after the neostigmine-atropine injections. Although one patient in each group spontaneously opened their eyes before the 10-min measurement interval was completed, BP and HR remained stable, and hence, their data were not excluded from the subsequent data analyses. All other patients in both groups did not open their eyes throughout the 10-min measurement period. In all patients, oxygen saturation values, measured by pulse oximeter, were more than 97%, end-tidal CO_2 tension was <45 mmHg, and rectal temperatures were between 37.5°C and 36.5°C during the 10-min observation periods.

Discussion

Although several previous studies have reported the effect of anesthetic agents on HR changes after neostigmine-atropine injections [1–3], to the best of our knowledge, the effects of propofol-based anesthesia on HR changes after intravenous injections of a neostigmine-atropine mixture have never been addressed. Our study demonstrated that propofol anesthesia attenuated the initial increases in HR, enhanced the subsequent decreases in HR, and increased the incidence of bradycardia after intraveous neostigmine-atropine administration compared with the effects of isoflurane anesthesia.

HR responses to intravenous atropine may differ considerably depending on the anesthetic agents and techniques used [9,11,12]. Although the precise mechanism for the divergent HR responses is yet to be determined, it is considered to reflect the effects of anesthetic agents on the balance between sympathetic and parasympathetic influence on the heart [9,11]. Cross et al. [9] showed that atropine-induced HR increases were significantly attenuated in patients anesthetized with propofol-fentanyl-N_2O compared with these HR increases in patients anesthetized with enflurane-fentanyl-N_2O, and they suggested that the attenuated HR increases during propofol-based anesthesia were associated with a relative predominance of vagal influences. Indeed, such an autonomic milieu associated with propofol has been explained by a central sympatholytic/vagotonic mechanism and/or by parasympathetic tone being reduced to a lesser degree than sympathetic tone [6,13]. On the other hand, even though isoflurane depresses both the sympathetic and parasympathetic components of the autonomic nervous system equally, recovery of autonomic function is known to occur relatively quickly after isoflurane anesthesia [14,15]. Therefore, it is conceivable that the more suppressed initial increase in HR in the propofol group than in the isoflurane group in our study can be ascribed to the relatively depressed state of the sympathetic nervous system after propofol anesthesia and/or to the relatively well preserved state of the sympathetic nervous system after isoflurane anesthesia.

Our fundings of the enhanced HR reduction and the increased incidence of bradycardia after neostigmine-atropine injection in the propofol group are in accordance with previous findings. Bradycardia during propofol anesthesia was reported in association with several drugs that can potentiate vagal tone, such as neostigmine and suxamethonium [7,8]. Deutschman et al. [6], by analyzing HR variability spectra, demonstrated that parasympathetic tone was reduced to a lesser degree than sympathetic tone throughout propofol anesthesia and they suggested that propofol anesthesia may predispose patients to develop bradycardia in response to parasympathetic stimuli.

The interpretation of our results should be confined to the combination doses used in our study. Mirakhur et al. [4] reported a 30% incidence of bradycardia (HR <50 beats·min^{-1}) when the combination of atropine 0.02 mg·kg^{-1} and neostigmine 0.05 mg·kg^{-1} was injected intravenously after halothane anesthesia. Naguib and Gomaa [16] reported that the atropine requirements to prevent neostigmine from lowering HR below baseline in 50% of patients were 0.031 mg·kg^{-1} for neostigmine 0.04 mg·kg^{-1}, and 0.033 mg·kg^{-1} for neostigmine 0.06 mg·kg^{-1} under nitrous oxide-halothane anesthesia; these values suggest that atropine 0.02 mg·kg^{-1}, when combined with neostigmine 0.05 mg·kg^{-1}, would have been insufficient to prevent bradycardia in most patients anesthetized with isoflurane in our study. Because the incidence of bradycardia in the propofol group in our study was more than double that in the isoflurane group, it is possible that a larger dose of atropine may be required to prevent bradycardia in patients anesthetized with propofol.

We observed close positive correlations between the preinjection HR and the minimum HR values after neostigmine-atropine injections in both groups in our study. The regression line in the propofol group was shifted toward right compared with that in the isoflurane group, even though preinjection HR values were similar in the two groups. These results suggest that close attention should be paid to HR changes after neostigmine-atropine injection, especially in patients anesthetized with propofol whose preinjection HR value is low.

The results of our study should be interpreted with some constraints. First, in our study, no stimulus was given to the patients during the 10-min measurement period. However, in standard clinical practice, some stimuli, including oropharyngeal suction, may be given after neostigmine-atropine administration, and this may prevent bradycardia during this period. Second, because the neostigmine-atropine mixture was injected immediately after the discontinuation of the anesthetic agents, the blood concentrations of the anesthetic agents must have been changing during the observation period. If the neostigmine-atropine mixture had been injected when anesthetic status was stable, the HR and BP changes could have been different from the present results. However, we intended to approximate the clinical situation, in which neostigmine-atropine mixture is injected when patients are about to emerge from general anesthesia. Third, fentanyl, with its intrinsic vagotonic activity, administered at induction and during anesthesia may have influenced the hemodynamic responses to the neostigmine-atropine mixture [17]. Fourth, because glycopyrrolate has been reported to provide a more stable HR than atropine when administered with neostigmine [1,4,5,18], the use of glycopyrrolate instead of atropine as an anticholinergic agent could have affected our results. Finally, because depth of anesthesia may affect the HR response to atropine via alterations in the vagal tone, it is imperative that an equivalent depth of anesthesia should have been achieved in both our groups. Even though direct comparison of anesthetic levels between volatile and intravenous agents may be difficult, similar BP and HR values in the two groups before the administration of the neostigmine-atropine mixture, as well as similar times from discontinuance of anesthetics until eye-opening and tracheal extubation in the two groups do not suggest that one anesthetic technique resulted in a considerably deeper level of anesthesia than the other at the time of the hemodynamic determinations.

In conclusion, propofol anesthesia attenuates the initial increases in HR, enhances the subsequent decreases in HR, and increases the incidence of bradycardia associated with the intravenous injection of a neostigmine $0.05\,mg\cdot kg^{-1}$-atropine $0.02\,mg\cdot kg^{-1}$ mixture compared with the effects of isoflurane anesthesia. Close attention should be paid after neostigmine-atropine injection in patients anesthetized with propofol, especially if their preinjection HR value was low.

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