

## Effects of Oral Clonidine on Heart Rate Changes after Neostigmine-Atropine Administration

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**Background:** Clonidine reduces heart rate (HR) responses to atropine, whereas neostigmine causes bradycardia. This study was designed to determine whether clonidine premedication would reduce tachycardia after neostigmine-atropine administration.

**Methods:** Fifty adult patients without cardiovascular disorders who were scheduled for elective surgeries were randomly assigned to receive approximately 5 µg/kg (oral clonidine clonidine group, n = 25) or no clonidine (control group, n = 25) 90 min before induction of general anesthesia. After tracheal intubation, anesthesia was maintained with N<sub>2</sub>O and 1-2% isoflurane in oxygen while patients were paralyzed with vecuronium and mechanically ventilated. When surgeries were completed, adequate spontaneous respiration, responses to verbal commands, and sustained tetanus by stimulating the ulnar nerve were confirmed, and patients' tracheas were extubated. Then a mixture of 0.05 mg/kg neostigmine and 0.02 mg/kg atropine was administered intravenously over 20 s under stable hemodynamic condition (systolic blood pressure and HR within ±5% of preceding values), and blood pressure and HR were measured noninvasively at 1-min intervals for 10 min.

**Results:** Increases in HR in the clonidine group were significantly less 1-4 min after neostigmine-atropine injections compared with HR values in the control group. A maximum increase in HR of the clonidine group was also significantly less than the control group ( $15 \pm 7$  vs.  $23 \pm 10$  beats/min; means ± SD), whereas absolute values of mean blood pressure were similar. Severe bradycardia (HR < 50 beats/min) developed in no patients in either group.

**Conclusions:** Premedication with 5 µg/kg oral clonidine attenuates the initial increases in HR without subsequent decreases in HR. (Key words: α<sub>2</sub>-adrenergic agonist; cholinester-

ase inhibitor; muscarinic antagonist; parasympathetic nervous system; sympathetic nervous system.)

ORAL clonidine has been used increasingly as premedication, because it reduces anesthetic requirements,<sup>1</sup> improves hemodynamic stability,<sup>2</sup> and potentiates postoperative analgesic regimens.<sup>3</sup> Previous studies have shown that 5 µg/kg clonidine given before operation attenuated heart rate (HR) increases to intravenous atropine,<sup>4</sup> suggesting that clonidine may attenuate initial tachycardic responses to a neostigmine-atropine mixture for antagonizing nondepolarizing muscle relaxants. On the other hand, clonidine is frequently associated with bradycardia and hypotension.<sup>5</sup> Clonidine may, therefore, augment subsequent bradycardic response after injection of neostigmine-atropine mixtures. To the best of our knowledge, the effects of clonidine premedication on hemodynamic changes resulting from the neostigmine-atropine mixture have not been addressed before.

### Materials and Methods

After the study protocol was approved by our local ethics committee and informed consent was obtained from each patient, 50 adult patients classified as American Society of Anesthesiologists physical class 1 or 2 and scheduled for elective surgeries under general anesthesia were studied. Patients with a history of cardiovascular disorders, diabetes, disorders known to affect autonomic functions, and those taking medications known to affect cardiovascular functions and whose resting HRs were <50 beats/min were excluded. The patients were randomly assigned to either the clonidine group (n = 25), who received approximately 5 µg/kg clonidine (Boehringer Ingelheim, Indianapolis, IN; each tablet contains 75 µg) plus 20 mg famotidine (an H<sub>2</sub>-blocker), or to the control group (n = 25), who received 20 mg famotidine alone orally 90 min before general anesthesia was induced.

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On arrival in the operating room, a 20-gauge intravenous cannula was inserted and lactated Ringer's solution was administered at a rate of  $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  throughout the study. Standard lead II electrocardiography (NEC San-ei Instrument Co., Tokyo, Japan) and an automated blood pressure (BP) cuff (BP-308ET, Nippon Colin Co., Tokyo, Japan) at the contralateral arm were applied. Heart rate was determined as an average of 4-s intervals recorded on the electrocardiography monitor, and mean BP (MBP) was calculated electronically. General anesthesia was induced with 5 mg/kg thiamylal, and tracheal intubation was facilitated with 0.2 mg/kg vecuronium given intravenously. All the patients' lungs were mechanically ventilated with 70% nitrous oxide and 1–2% end-tidal isoflurane in oxygen during surgical procedures. No additional vecuronium or other anesthetics were administered during surgeries. At the completion of surgery, the presence of a response to a verbal command, sustained muscle contracture for 5 s to tetanus stimulus at 50 Hz to the ulnar nerve, spontaneous respiration with end-tidal carbon dioxide tensions  $<45 \text{ mmHg}$ , and end-tidal isoflurane concentrations  $<0.2\%$  were confirmed, and then patients' tracheae were extubated. After obtaining stable BP and HR (systolic BP and HR within  $\pm 5\%$  of the preceding values) for at least 5 min and pulse oximetry readings  $>96\%$  with supplemental oxygen, 3 l/min *via* face mask, a mixture of 0.05 mg/kg neostigmine and 0.02 mg/kg atropine was given intravenously over 20 s. Measurements of BP and HR were made at 1-min intervals for 10 min after neostigmine-atropine injection, and after 10 min later.

All data are expressed as means  $\pm$  SD. Patient characteristics were compared using unpaired Student's *t* test. Blood pressure and HR responses to the neostigmine-atropine mixture over time were analyzed by repeated-measures analysis of variance followed by Fisher's protected least-significant difference method as a *post hoc* test to analyze group differences. A *P* value  $<0.05$  was considered significant.

## Results

Each study group consisted of 14 men and 11 women. There were no significant differences between the control and clonidine groups in terms of age ( $45 \pm 15 \text{ yr}$  *vs.*  $43 \pm 15 \text{ yr}$ ), weight ( $58 \pm 15 \text{ kg}$  *vs.*  $60 \pm 8 \text{ kg}$ ), height ( $163 \pm 8 \text{ cm}$  *vs.*  $163 \pm 8 \text{ cm}$ ), and duration of surgery ( $91 \pm 57 \text{ min}$  *vs.*  $114 \pm 76 \text{ min}$ ). The average

dose of clonidine in the clonidine group was  $4.7 \pm 0.2 \text{ } \mu\text{g/kg}$ . There were also no significant differences between groups in resting MBP ( $85 \pm 9 \text{ mmHg}$  *vs.*  $85 \pm 14 \text{ mmHg}$ ) and resting HR ( $68 \pm 17 \text{ beats/min}$  *vs.*  $69 \pm 8 \text{ beats/min}$ ). After clonidine premedication, both MBP and HR significantly decreased ( $78 \pm 8 \text{ mmHg}$  and  $62 \pm 10 \text{ beats/min}$ , respectively;  $P < 0.05$ ) compared with resting values, whereas in the control group, MBP and HR were unchanged ( $84 \pm 10 \text{ mmHg}$  and  $71 \pm 13 \text{ beats/min}$ , respectively). The types of surgeries were otolaryngeal, orthopedic, or gynecologic.

No significant differences in preinjection HR and MBP were seen between the groups. Preinjection HR in the control group was significantly higher than the resting and preinduction HR values ( $P < 0.01$ ). In addition, preinjection HR in the clonidine group was significantly higher than the preinduction (after clonidine premedication) value ( $P < 0.01$ ) but was similar to the resting value. Injections of the neostigmine-atropine mixture produced a similar hemodynamic pattern in both groups, initial increases, and then subsequent decreases in both HR and MBP (table 1). However, absolute HR values and changes in HR were significantly different between groups ( $P = 0.007$  and  $P = 0.019$ , respectively, by repeated-measures analysis of variance). Compared with the control group, absolute HR values in the clonidine group were significantly less between 1 and 5 min and between 7 and 9 min after injections. In addition, increases in HR from baseline values of the clonidine group were significantly less than those of the control group 1–4 min after injections. Furthermore, a maximum increase in HR of the clonidine group was significantly less than that of the control group ( $15 \pm 7 \text{ beats/min}$  *vs.*  $23 \pm 10 \text{ beats/min}$ ,  $P = 0.03$ ). On the other hand, there were no significant differences in absolute MBP values and changes in MBP between groups ( $P = 0.29$  and  $P = 0.30$ , respectively, by repeated-measures analysis of variance). No patient in either group developed severe bradycardia (HR  $<50 \text{ beats/min}$ ) during the study period.

## Discussion

Our data showed that clonidine attenuated initial increases but did not enhance subsequent decreases in HR with minimal effects on BP on neostigmine-atropine injections. These results suggest that  $5 \text{ } \mu\text{g/kg}$  clonidine given before operation is well tolerated hemodynamically at the time of antagonizing, nondepolarizing



## EFFECT OF CLONIDINE AND NEOSTIGMINE ON HEART RATE

Table 1. Mean Blood Pressure and Heart Rate Values after Neostigmine 0.05 mg/kg and Atropine 0.02 mg/kg Administration

		Time after Neostigmine-Atropine Injection (min)											
		Baseline	1	2	3	4	5	6	7	8	9	10	20
Control group (n = 25)	MBP	89 ± 10	92 ± 11	90 ± 9	88 ± 10	88 ± 10	86 ± 10	85 ± 11	85 ± 11	84 ± 12	84 ± 10	82 ± 10	89 ± 11
	HR	81 ± 10	101 ± 12	99 ± 13	92 ± 13	86 ± 14	81 ± 13	78 ± 13	77 ± 13	77 ± 15	74 ± 13	71 ± 19	68 ± 10
Clonidine group (n = 25)	MBP	90 ± 9	97 ± 12	93 ± 11	90 ± 11	90 ± 11	90 ± 11	89 ± 11	88 ± 11	89 ± 11	86 ± 13	86 ± 11	88 ± 10
	HR	74 ± 13	87 ± 13*	84 ± 14*	78 ± 13*	74 ± 12*	72 ± 12*	71 ± 11	70 ± 11*	68 ± 11*	67 ± 12*	66 ± 10	65 ± 10

Values are mean ± SD.

MBP = mean blood pressure (mmHg); HR = heart rate (beats/min).

\*  $P < 0.05$  versus the control group.

muscle relaxants in otherwise healthy patients. This open-labeled study was conducted in healthy patients to generate data to be used in a future study in those with a history or risks of coronary artery disease with ST-T monitoring, in whom the beneficial effects of clonidine are likely to outweigh adverse effects.<sup>6</sup> One limitation of our study would be that our findings are confined to the current drug combination and the dosages studied. 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,<sup>7</sup> is recommended in clinical anesthesia when combined with neostigmine, because smaller doses of atropine produces unacceptable decreases in HR, whereas larger doses are associated with a greater incidence of dysrhythmia.<sup>8</sup> Using glycopyrrolate instead of atropine as an anticholinergic agent could have produced different results. Whether smaller doses of clonidine would result in similarly favorable hemodynamic responses remains to be seen. One might also argue that HR response to atropine was modulated by volatile anesthetic agents.<sup>9,10</sup> In our study, <0.2% end-tidal isoflurane was confirmed before neostigmine-atropine injections in all patients. At this concentration of isoflurane, the effects of isoflurane on hemodynamic changes by atropine would be minimized, although not confirmed, previously. Finally, neostigmine and atropine were administered simultaneously in our study, and thus the effects of clonidine on hemodynamic changes by neostigmine, *per se*, were not clear from our results.

Significantly higher preinjection HR values compared with the resting and preinduction values in the control group, and compared with the preinduction value in the clonidine group suggest some sympathetic activation or parasympathetic deactivation occurred during the early emergence period. Based on the fact that the

onset of hemodynamic changes due to atropine is much faster than that of neostigmine, the initial tachycardic response after neostigmine-atropine injection is considered primarily as the effect of atropine. Our results showing that initial increases in HR were significantly suppressed after parasympathetic withdrawal by atropine in the clonidine group suggests either that sympathetic nervous activity in the clonidine group was still partially depressed with comparable parasympathetic activity between groups, or that preoperative clonidine preserved basal parasympathetic nervous activity at the time the study drug were injected. Alternatively, a total abolition of parasympathetic activity by atropine may have been prevented by clonidine, because baseline hemodynamic variables were comparable between the groups (table 1), suggesting that the balance of baseline sympathetic *versus* parasympathetic nervous system activities were also similar.<sup>11</sup> Investigating each component of the autonomic nervous system using HR variability, baroreflex functions, or both may help to elucidate a more precise mechanism of clonidine in attenuating HR response to atropine.<sup>12</sup>

Our data also showed that clonidine did not enhance subsequent reductions in HR, which are regarded primarily as the effect of intravenous neostigmine. Although we did not measure plasma clonidine concentrations, previous pharmacokinetic studies have shown that plasma concentration increases rapidly after a single oral dose of clonidine and reached nearly 80% of the peak plasma level after 1.5 h.<sup>13,14</sup> In addition, the elimination half-life of approximately 10 h suggests that significant plasma clonidine concentrations were still maintained at the time of hemodynamic determinations.<sup>12</sup> Indeed, the effects of preoperative clonidine were evident in lower HRs during most study intervals and significantly suppressed HR responses to atropine



during the early study period in the clonidine-treated patients. It is conceivable that clonidine does not further accentuate bradycardia *via* a peripheral muscarinic effect of intravenous neostigmine.

In conclusion, oral premedication with 5  $\mu$ g/kg clonidine attenuates initial increases in HR but does not enhance subsequent decreases in HR after intravenous neostigmine-atropine injections in healthy adult patients after isoflurane anesthesia.

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