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SHORT COMMUNICATION

Can intravenous atropine prevent bradycardia and hypotension during induction of total intravenous anesthesia with propofol and remifentanil?

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Abstract This study was conducted to examine whether pretreatment with intravenous atropine could prevent bradycardia and hypotension during induction of total intravenous anesthesia with propofol and remifentanil in a prospective randomized placebo-controlled manner. Seventy patients, aged 24–78 years, were randomly divided into two groups, and received 0.5 mg atropine or placebo saline 1 min before induction of intravenous anesthesia with remifentanil at 0.4 μg/kg/min, propofol at a target blood concentration of 3 μg/ml, and vecuronium 1.5 mg/kg. Immediately after tracheal intubation, the infusion rate of remfentanil and the target concentration of propofol were reduced to and kept at 0.1 μg/kg/min and 2 μg/ml, respectively, for 10 min. Noninvasive blood pressure (BP) and heartrate (HR) were measured and recorded every minute. Intravenous atropine could prevent a fall in HR, but not a fall in BP, during induction of intravenous anesthesia with propofol and remifentanil of our dosing regimen. Our data suggested that a fall in HR induced by propofol–remifentanil anesthesia was mainly caused by centrally mediated sympatholytic and/or vagotonic actions of propofol and remifentanil, whereas a fall in BP was mainly the result of their direct vasodilating actions.

Keywords Atropine · Propofol · Remifentanil · Hypotension · Bradycardia

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Bradycardia and hypotension are commonly encountered adverse effects of total intravenous anesthesia with propofol and remifentanil. The hemodynamic instability caused by this anesthetic regimen could be critical [1]. These adverse effects are at least partly the result of the centrally mediated vagotonic and/or sympatholytic action of remifentanil [2, 3] and the centrally mediated sympatholytic action of propofol [4].

We usually use intravenous atropine for treatment of bradycardia. However, several possibilities exist that intravenous (IV) atropine administration can lead to increase of blood pressure (BP). Atropine blocks the resting muscarinic tone of the parasympathetically dominated heart, which causes an unopposed tone-up in the sympathetic system with increase of heartrate (HR) [5]. Increased HR could result in increased cardiac output and BP. Therefore, we suspect that pretreatment with intravenous atropine administration can be effective not only for attenuation of bradycardia but also for prevention of hypotension, especially in parasympathetic dominant status under propofol–remifentanil anesthesia.

We thus conducted the present prospective randomized placebo-controlled study to evaluate if IV atropine could prevent bradycardia and hypotension during induction of propofol–remifentanil anesthesia in adults.

With institutional human study ethics committee approval and informed consent, 70 adult patients (31 men and 39 women), aged 24–78 years, classified as ASA I or II, and scheduled to undergo noncardiac surgery under general anesthesia, were enrolled. Patients were randomly allocated into the atropine group or the placebo group.

Patients were kept in supine position and oxygenated with 6 l oxygen via face mask for several minutes. Crystalloids were infused rapidly by free-fall without clump through the 20-gauge venous cannulae, concurrently with

Table 1 Patient demography and vasoactive agent requirements

Group	Placebo group	Atropine group
Age (years)	54 ± 15	57 ± 15
Male/female	15/20	16/19
Body height (cm)	161 ± 8	160 ± 9
Body weight (kg)	61 ± 12	60 ± 14
ASA class (1/2)	19/16	14/21
Prop-Vec time (min)	3.5 ± 1.5	3.8 ± 1.5
Prop-IT time (min)	7.7 ± 2.4	7.8 ± 1.8
No. of patients who received ephedrine	11	10
Ephedrine dose (mg)	7.6 ± 3.9 ($n = 11$)	6.7 ± 2.1 ($n = 10$)
No. of patients who received atropine	0	0

Prop-Vec time, time from the start of propofol infusion to the vecuronium injection; Prop-IT time, time from the start of propofol infusion to completion of tracheal intubation

the oxygenation. Anesthesia was induced with routine monitoring, including three-lead electrocardiogram and noninvasive BP (Intellivue MP 60; Phillips Electronics, Japan), as follows. (1) Atropine sulfate (0.5 mg in 1 ml) or normal saline (1 ml) was IV injected en bolus. (2) One minute after the test drug injection, IV infusion of remifentanil at a rate of 0.4 μg/kg/min was commenced using a syringe infusion pump. (3) One minute after the start of remifentanil infusion, IV infusion of propofol, targeted to blood concentration of 3 μg/ml, was commenced using a target-controlled infusion (TCI) pump (TE-371; Terumo, Tokyo, Japan). (4) After loss of consciousness, the lungs were manually ventilated, and then vecuronium bromide (0.15 mg/kg) was IV injected. (5) Three minutes after vecuronium injection, the trachea was intubated. (6) Just after tracheal intubation, the infusion rate of remifentanil and the target concentration of propofol were reduced to 0.1 μg/kg/min and 2 μg/ml, respectively, and the drugs were infused at these doses for 10 min.

Because time from the start of propofol infusion to completion of tracheal intubation varied among patients, BP and HR only at the following nine time points were analyzed: at the time of the test drug injection (T0, baseline); at the start of remifentanil infusion (T1); at the start of propofol infusion (T2); at 1 min after the start of propofol infusion (T3); at the time of vecuronium injection (T4); immediately before tracheal intubation (T5); immediately after tracheal intubation (T6); at 5 min after tracheal intubation (T7); and at 10 min after tracheal intubation (T8). Whenever systolic BP decreased to less than 80 mmHg during the observation period, ephedrine (4 mg) was IV injected. Whenever HR decreased to less than 40 beats per minute (bpm), atropine sulfate (0.5 mg) was IV injected.

Data are presented as the number of patients or mean ± SD. Statistical analyses were performed with Fisher's exact test or unpaired t test to examine intergroup differences, and with repeated-measures analysis of variance (ANOVA), followed by post hoc testing with Fisher's probability of least significant difference test if indicated, to examine intragroup differences. $P < 0.05$ was considered statistically significant.

There were no differences between the groups in demographic data, time from the start of propofol infusion to vecuronium injection, time from the start of propofol infusion to completion of tracheal intubation, or the requirement of atropine or ephedrine (Table 1).

In the placebo group, HR decreased significantly at T4 through T8, compared with baseline, whereas in the atropine group, it increased significantly at T2, T3, and T4 and returned to baseline at T5. HR was higher at T3 through T8 in the atropine than the placebo group (Fig. 1). In both groups, systolic BP decreased significantly at T3 through T8, compared with baseline, and it was significantly higher only at T5 in the atropine than in the placebo group (Fig. 2). In both groups, diastolic BP decreased significantly at T4 through T8, compared with baseline, and there was no difference in diastolic BP between the groups throughout the observation period (Fig. 2).

Most organs of the body receive dual innervation from the sympathetic and parasympathetic systems. The responses elicited in effector organs are frequently opposite between sympathetic and parasympathetic stimulation. One of two systems normally exhibits dominant activity in the organ's function, which provides the "resting tone" of the organ function [5]. In the heart, the frequency of contraction increases by adrenergic response associated with sympathetic stimulation. On the other hand, it decreases by cholinergic response elicited by excitement of parasympathetic system, which is dominant in resting [5]. Excessive dominance of the parasympathetic system caused by administration of remifentanil and propofol might cause

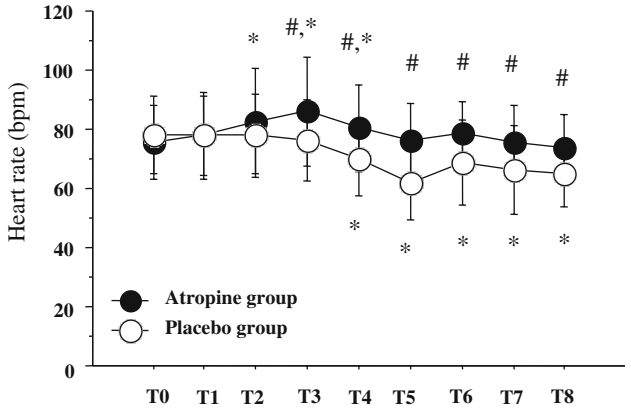

Fig. 1 Changes in heart rate during induction of anesthesia in the atropine (*black circles*) and placebo (*white circles*) groups. $^{*}P < 0.05$, compared with T0 (baseline); $^{\#}P < 0.05$, compared with the placebo group. *T0*, before administration of test drugs (baseline); *T1*, at the start of remifentanil infusion; *T2*, at the start of propofol infusion; *T3*, at 1 min after the start of porpofol infusion; *T4*, at the time of vecuronium injection; *T5*, immediately before tracheal intubation; *T6*, immediately after tracheal intubation; *T7*, at 5 min after tracheal intubation; *T8*, at 10 min after tracheal intubation

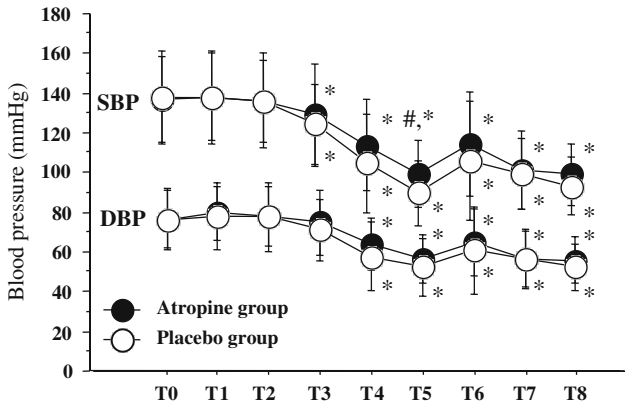

Fig. 2 Changes in blood pressure during induction of anesthesia in the atropine (*black circles*) and the placebo (*white circles*) groups. $^{*}P < 0.05$, compared with T0 (baseline), $^{\#}P < 0.05$, compared with group P. *T0*, before administration of test drugs (baseline); *T1*, at the start of remifentanil infusion; *T2*, at the start of propofol infusion; *T3*, at 1 min after the start of porpofol infusion; *T4*, at the time of vecuronium injection; *T5*, immediately before tracheal intubation; *T6*, immediately after tracheal intubation; *T7*, at 5 min after tracheal intubation; *T8*, at 10 min after tracheal intubation; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure

critical bradycardia. One multicenter study reported that frequency of hypotension and bradycardia were estimated to be 10–30% and 7–19%, respectively, depending on the dose of remifentanil during anesthetic induction and maintenance [6]. The degree of hypotension was estimated to be a 26–31% reduction, compared with preanesthetic values [6]. All opioids can decrease BP as a result of centrally mediated reductions in sympathetic tone and/or a direct vasodilating action on the vascular smooth muscle [2, 3]. All opioids except meperidine decrease HR, and sometimes induce bradycardia with HR as low as 30–40 bpm, primarily by means of centrally mediated vagal stimulation [3]. Propofol consistently decreases BP via centrally mediated reductions in sympathetic tone and/or direct vasodilating action on the vascular smooth muscle, whereas the effect of propofol on HR is inconsistent [4]. When used together, hemodynamic effects of propofol and remifentanil can be additive or synergistic [6].

The present study revealed that pretreatment with IV atropine could prevent a fall in HR. After induction of propofol–remifentanil anesthesia, however, BP decreased significantly, compared with baseline, irrespective of pretreatment with atropine, and systolic BP was significantly but slightly higher with atropine than with placebo only immediately before tracheal intubation. These data indicated that pretreatment with IV atropine at a dose that totally prevented a fall in HR could barely prevent a fall in BP.

To our knowledge, there are only two previous studies from the same group of investigators that evaluated the effect of pretreatment with IV atropine on hemodynamics in subjects anesthetized with general anesthesia incorporating remifentanil [7, 8]. In the first study from the group, remifentanil produced falls in BP and HR when it was added to stable sevoflurane anesthesia at one minimum alveolar concentration (MAC) in children, and IV atropine could not prevent a fall in BP caused by remifentanil, whereas it could prevent a fall in HR, which is consistent with our results [8]. The results of the present study suggested that a fall in HR induced by propofol–remifentanil anesthesia was mainly caused by centrally mediated sympatholytic and/or vagotonic actions of propofol and remifentanil, whereas a drop in BP was mainly the result of their direct vasodilating actions. These data suggest that hypotension caused by propofol–remifentanil anesthesia should be prevented or treated not with atropine but with vasopressor agents, whereas bradycardia can be prevented or treated with IV atropine.

On the other hand, in the second previous study from the same group, IV atropine could not totally prevent a fall in HR induced by remifentanil in children when remifentanil was added to stable 1-MAC sevoflurane anesthesia, although it could completely inhibit remifentanil-induced parasympathetic stimulation as evaluated by the high-frequency component of HR variability [8]. Although it is not known why the effect of IV atropine on remifentanil-induced decrease in HR was different between the two previous studies employing the same study design, the second previous study suggested that not only vagal stimulation but also a direct negative chronotropic effect on the heart contributed to the bradycardic action of remifentanil,

because the parasympathetic inhibition by atropine could not totally prevent its bradycardic effect [7, 8]. Therefore, a possibility exists that pretreatment with IV atropine cannot always effectively prevent or treat remifentanil-induced bradycardia when remifentanil is administered in a high dose.

In conclusion, prophylactic IV administration of 0.5 mg atropine prevented a fall in HR during induction of anesthesia with propofol and remifentanil. However, hypotension caused by propofol–remifentanil anesthesia could not be effectively prevented or treated with atropine insofar as moderate doses of these drugs are used.

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