Does Preoperative Oral Clonidine Inhibit Salivary Secretion during General Anesthesia?

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Clonidine is known to inhibit salivary secretions and cause dryness of the mouth. We evaluated the effect of preoperative oral clonidine on salivary secretions before and during general anesthesia. Twenty-eight adult patients, equally divided into four groups, received the following premedication 2 hr prior to induction of anesthesia. Group 1 patients received oral ranitidine 5 mg·kg^{-1} alone. Groups 2 and 3 patients received oral clonidine 1 μg·kg^{-1} and 3 μg·kg^{-1} respectively with oral ranitidine 5 mg·kg^{-1}. Group 4 patients received no premedication and served as control. The volume of salivary secretions was determined by calculating the change in weight of four cotton wool cylinders placed in the oral space 10 min before and 30, 60 and 120 min after induction of anesthesia. Salivary volume was significantly less in the clonidine treatment groups before induction of anesthesia. After induction of anesthesia, there were no significant differences in salivary secretions among the four groups. No severe hypotention or bradycardia was seen in any patient of four groups. Preoperative oral ranitidine 5 mg·kg^{-1} had no effect on salivary secretion. In conclusion, clonidine did not decrease salivary secretions further over the already decreased level during general anesthesia. (Key words: preoperative oral clonidine, salivary secretion, general anesthesia)

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Clonidine, an alpha 2 adrenergic receptor agonist and central antihypertensive agent, has been shown to suppress central noradrenergic activity and to have sedative and analgesic properties[1,2]. Previous reports demonstrate that clonidine attenuates reflex cardiovascular responses to tracheal intubation, improves perioperative hemodynamics and reduces anesthetic requirements[3–6]. Moreover, clonidine has been reported to have an analgesic effect when administered by the extradural or intrathecal route[7,8]. These properties are of potential benefit in anesthetic managements. However, clonidine also has an inhibitory action on salivary secretions[9–11]. Although the inhibitory action on salivary secretions is considered to be one of the major undesirable side effects of clonidine, it may be advantageous during the induction and maintenance of general anesthesia, but has never been

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Table 1. Patients' characteristics

		group 1	group 2	group 3	group 4
N		7	7	7	7
dose of clonidine		none	1 $\mu g \cdot kg^{-1}$	3 $\mu g \cdot kg^{-1}$	none
dose of ranitidine		5 $mg \cdot kg^{-1}$	5 $mg \cdot kg^{-1}$	5 $mg \cdot kg^{-1}$	none
age	(yr)	51 ± 5	45 ± 1	44 ± 9	52 ± 7
body weight	(kg)	54 ± 9	59 ± 4	50 ± 7	57 ± 7
height	(cm)	160 ± 6	158 ± 7	159 ± 5	158 ± 9
duration of anesthesia	(min)	230 ± 168	239 ± 41	216 ± 99	189 ± 65

mean ± SD

evaluated. Therefore, in this study, we examined the action of preoperative clonidine and ranitidine on salivary volume before and during anesthesia.

Materials and Methods

Twenty-eight ASA physical status 1–2 patients ranging in age from 20–60 yr and who were scheduled for a variety of surgical procedures were studied after approval of Hokkaido University Hospital Human Ethics Committee and after obtaining informed consent. Patients were randomly and equally divided into four groups; Group 1 patients received oral ranitidine 5 $mg \cdot kg^{-1}$ alone. Groups 2 and 3 patients received oral clonidine 1 $\mu g \cdot kg^{-1}$ and 3 $\mu g \cdot kg^{-1}$, respectively. Patients in groups 2 and 3 were also given oral ranitidine 5 $mg \cdot kg^{-1}$. Premedication were given two hr prior to induction of anesthesia. Group 4 patients received no premedication and served as control.

On arrival in the operating room, an IV catheter was inserted. Monitors included ECG, blood pressure, pulse oximetry, and capnography. The salivary volume was measured 10 min before, and 30 min, 60 min and 120 min after induction of anesthesia. Four dental cotton wool cylinders (Roller Cotton) were placed in the mouth, one in each buccal pouch and one on either side of the tongue[9]. The diameter of each cotton cylinder was 9 mm, and the length was 25 mm. They were left in place for one minute to absorb saliva already present and were then discarded. A second set of four weighed cotton wool cylinders was then put in position for 60 sec then re-weighed immediately following removal. The change in weight of the cotton wool cylinders was recorded. A third set was then put in position for the same period to provide a duplicate measurement.

Anesthesia was induced with thiamylal (5 $mg \cdot kg^{-1}$) and vecuronium (0.1–0.15 $mg \cdot kg^{-1}$) was given to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide 3 $l \cdot min^{-1}$, oxygen 2 $l \cdot min^{-1}$, and 0.5–2 MAC of either enflurane, isoflurane or sevoflurane. Arterial oxygen saturation (Sp_{O_2}) and end tidal CO_2 (ET_{CO_2}) were maintained at 98–100% and 4.0–4.5%, respectively during mechanical ventilation.

All values were expressed as mean ± SD unless otherwise stated. Statistical analyses were performed using a paired Student's t-test to analyze progressive changes within each group. An analysis of variance (ANOVA) was used to determine if there were significant differences among groups. A probability value of less than 0.05 was considered statistically significant.

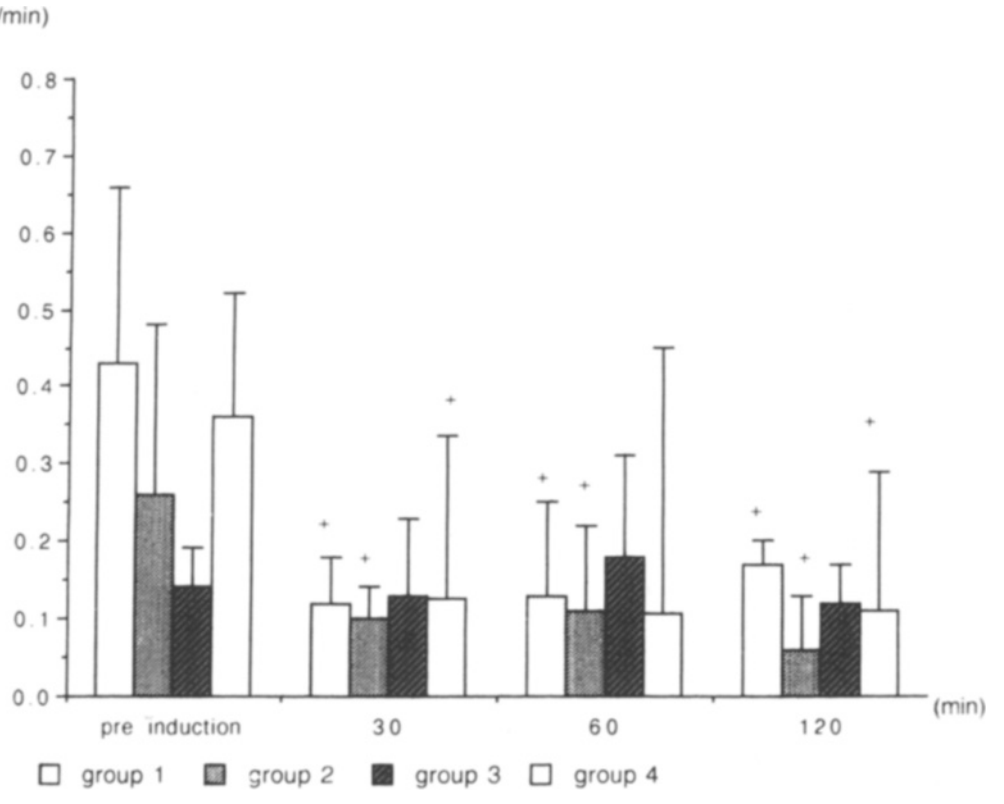

Fig. 1. Comparison of mean salivary volume in four groups.
Results are presented as mean values ± SEM of seven patients in each group. *indicates significant difference; group 2 vs group 1. **indicates significant difference; group 3 vs group 2. +indicates significant difference when each value is compared with a pre-induction value within a group.

Results

There were no significant differences in age, body weight, or duration of anesthesia (table 1).

Salivary volume differed significantly among the groups 10 min before induction of anesthesia. The mean values were 0.43 ± 0.23 (g) in group 1, 026 ± 0.22 (g) in group 2, 0.14 ± 0.05 (g) in group 3, and 0.36 ± 0.16 (g) in group 4. The volume of salivary secretions was significantly larger in group 1 patients than in group 2 patients. Similarly, the volume in the group 2 was larger than that in group 3. There was no significant difference in salivary volume between groups 1 and 4 and there were no significant difference in salivary volume among the four groups 30 min, 60 min, 120 min, after induction of anesthesia. Compared to pre-induction values, the volume of salivary secretions was significantly decreased by 72% in group 1, 65% in group 2 and 68% in group 4 ($P < 0.05$) 30 min after induction of anesthesia. However, salivary volume in each group almost remained the same from 30–120 min after induction of anesthesia (fig. 1).

Mean arterial blood pressure was significantly lower in group 3 (clonidine 3 $\mu g \cdot kg^{-1}$) compared to other groups prior to the induction of anesthesia. There were no significant

Table 2. Hemodynamic effects of clonidine premedication

	Group	pre-induction	Time after induction of anesthesia (min)		
			30	60	120
MAP (mmHg)	group 1	90 ± 9	98 ± 12	96 ± 16	94 ± 14
	group 2	92 ± 8	94 ± 10	93 ± 12	92 ± 9
	group 3	78 ± 9*	89 ± 11	87 ± 17	85 ± 13
	group 4	92 ± 11	97 ± 12	95 ± 13	93 ± 14
HR (beat·min^{-1})	group 1	76 ± 7	87 ± 12	87 ± 12	85 ± 10
	group 2	74 ± 7	86 ± 16	84 ± 13	83 ± 12
	group 3	70 ± 5	87 ± 12	82 ± 17	79 ± 13
	group 4	75 ± 8	87 ± 10	85 ± 15	86 ± 9

(mean ± SD)

MAP = mean arterial pressure.
HR = heart rate.
*indicates significant difference; group 3 vs group 1, 2, and 4.

differences in blood pressure among the groups 30, 60 and 120 min after induction of anesthesia. There were no significant differences in heart rate among four groups at any time (table 2).

Discussion

The results of this study indicate that clonidine does not change salivary volume further over the already decreased level after induction of anesthesia. The principal glands of salivation are the parotid, submandibular, and sublingual glands. The daily secretion of saliva normally ranges between 800 and 1,500 ml. Salivary glands are controlled mainly by parasympathetic nervous signals from the salivatory nuclei at the junction of the medulla and pons.

Clonidine is known to inhibit salivary secretions and cause dryness of the mouth. The mechanism by which clonidine affects salivation is considered to be both central and peripheral. At the salivary center in the brain stem, clonidine is believed to bind to post-synaptic alpha 2 adrenoreceptors in a manner similar to its proposed hypotensive action[12,13]. Green et al. have suggested that clonidine also acts at peripheral presynaptic adrenoreceptors and inhibits cholinergic transmission[14,15].

In this study, the inhibitory effect on salivary secretions was seen only prior to the induction of anesthesia. The salivary volumes in groups 2 and 3 (1 μg·kg^{-1} and 3 μg·kg^{-1} of oral clonidine, respectively) were less when compared with those in groups 1 and 4. After general anesthesia was induced, there was no significant difference in salivary volume among the four groups. In each group, three patients were given isoflurane, two were given enflurane, and two were given sevoflurane. It is conceivable that anesthetic agents, including barbiturate, isoflurane, enflurane and sevoflurane, have a central neural action that affects salivary secretions at the brain stem level. Thus, the inhibitory effect of clonidine may be not evident when secretion is already at a low level, such as during general anesthesia.

We administered only small doses of clonidine (1 μg·kg^{-1}, 3 μg·kg^{-1}). Carabine, et al. demonstrated that in adults oral clonidine 0.2 mg provided anxiolysis without any cardiovascular

side effects, including avoiding severe hypotention and bradycardia[16]. Our results also demonstrated that clonidine (1 $\mu g \cdot kg^{-1}$ and 3 $\mu g \cdot kg^{-1}$) did not cause severe hypotention or bradycardia during general anesthesia.

We routinely administer ranitidine, a H_2-blocker, in order to reduce the risk of pulmonary acid aspiration by decreasing the acidity and volume of gastric fluid[17,18]. Patients in groups 1, 2 and 3 were given ranitidine 5 $mg \cdot kg^{-1}$ as premedication 2 hr prior to induction of anesthesia. In order to exclude the possibility that ranitidine reduces salivary secretions, patients in group 4 were given no premedication and served as control. There was no significant difference in salivary secretions between groups 1 and 4. There have been no reports of ranitidine reducing salivary secretions. Therefore, in this study the reduction in salivary secretions prior to the induction of anesthesia was most likely due to clonidine.

In summary, we studied volume changes in salivary secretions before and during general anesthesian in 28 adult patients. The reduction of salivary secretions by clonidine premedication was seen in a dose dependent manner only before induction of anesthesia. During general anesthesia, the effect of 1 and 3 $\mu g \cdot kg^{-1}$ of oral clonidine on salivary secretions was not detectable, that is, the levels of salivary secretion were already at a very low level during anesthesia in these patients.

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