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Clonidine premedication for sevoflurane anesthesia in upper abdominal surgery

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Abstract: The effects of clonidine as a preanesthetic medication were compared with diazepam on clinical courses of sevoflurane anesthesia in 22 patients undergoing upper abdominal surgery. The patients were divided into two groups of 11 patients each according to preanesthetic medication: atropine 0.5 mg i.m. plus clonidine 0.3 mg p.o., or atropine 0.5 mg i.m. plus diazepam 10 mg p.o. 60–90 min prior to induction of anesthesia. Anesthesia was induced with fentanyl and thiopental, and was maintained with sevoflurane, 0.5%–1.5%, nitrous oxide and oxygen, supplemented with fentanyl, 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. While only one patient needed a vasodilator in the clonidine group for treatment of hypertension, seven patients needed it in the diazepam group. Pain score after extubation was higher in the diazepam group than in the clonidine group. The time when patients responded to verbal command after discontinuation of anesthetics was similar in both groups. Therefore, clonidine pretreatment was useful for sevoflurane anesthesia in upper abdominal surgery.

Key words: Volatile anesthetics, Sevoflurane, Pharmacology, Clonidine, Upper abdominal surgery, Premedication

Introduction

Sevoflurane has a low blood solubility and its blood level is easily controllable [1–4]. Although the fast recovery from anesthesia permits a short stay in the hospital in the case of anesthesia for outpatients [5], pain may occur in the very early postoperative period if adequate pain control is not performed. We previously clarified that the reactive capability of the feline central nervous system to peripheral stimulation was not notably affected or augmented by sevoflurane [6]. This weak suppressive action of sevoflurane on central nervous system response may be reflected by labile hemodynamics in response to surgical manipulation during sevoflurane anesthesia. Clonidine, a centrally acting α_2-adrenoceptor agonist, has been shown to attenuate reflex cardiovascular response to tracheal intubation [7–11] and surgical manipulation [7–14], and is often used as a preanesthetic medication to stabilize intraoperative hemodynamics, especially in hypertensive patients [7,8]. It also has sedative properties and analgesic effects and is reported to reduce anesthetic requirements [7–14]. We suspect that premedication with clonidine will stabilize intraoperative hemodynamics, alleviate early postoperative pain, and reduce excitement at recovery from anesthesia, while the time of recovery from sevoflurane anesthesia is not affected. To clarify this hypothesis, we compared preanesthetic regimens of clonidine with diazepam in patients undergoing elective upper abdominal surgery with sevoflurane anesthesia.

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Materials and methods

The study had the approval of the Institutional Human Studies Committee, and oral informed consents were obtained from all 22 patients scheduled to undergo elective upper abdominal surgery. The patients (5 women and 17 men, 33–61 years of age) weighed 33–77 kg, were ASA physical status 1 or 2, and had not taken medications known to affect anesthetic depth or MAC. They were randomly assigned to two groups consisting of 11 patients each, according to preanesthetic medication: either clonidine 0.3 mg p.o. plus atropine 0.5 mg i.m. or diazepam 10 mg p.o. plus and atropine 0.5 mg i.m., administered 60–90 min prior to induction of anesthesia. A nasogastric tube and a Foley catheter were inserted. On arrival in the operating room, intravenous and radial artery catheters were percutaneously

inserted under local anesthesia. Anesthesia was induced intravenously with 2 $\mu g \cdot kg^{-1}$ of fentanyl, 3–4 $mg \cdot kg^{-1}$ of thiopental, and 0.1 $mg \cdot kg^{-1}$ of pancuronium followed by endotracheal intubation. Following tracheal intubation, anesthesia was maintained with sevoflurane, 0.5%–1.5%, and N_2O/O_2 (65%/35%), supplemented with fentanyl, 0.5 $\mu g \cdot kg^{-1}$ i.v. at 1-h intervals. When blood pressure increased to more than 50 mmHg over the premedication value, the inspired concentration of sevoflurane was increased to 1.5%; if blood pressure was still greater than 50 mmHg after 10 min, nicardipine 0.5–1 mg i.v., or nifedipine 10 mg intranasally, was administered. Pancuronium was added if needed. At the end of surgery, discontinuation of sevoflurane was followed by reversal of muscle relaxation with neostigmine 2.5 mg i.v. combined with atropine 1.0 mg i.v. and then nitrous oxide was discontinued after confirming reversal of muscle relaxation. Postoperatively, the analgesics pentazocine 15 mg i.m. or buprenorphine 0.15 mg i.m. were administered if needed.

Measurements of the arterial blood pressure and heart rate were recorded at the following points: (1) prior to preanesthetic medication in the ward, (2) prior to induction of anesthesia, (3) after induction of anesthesia (before tracheal intubation), (4) within 2 min after tracheal intubation, (5) just before skin incision, (6) 5 min after skin incision, (7) 10 min after skin incision, and (8) upon arrival in the recovery room. The level of sedation was assessed on arrival in the operating room and within 5 min after tracheal extubation using the following score: 0, excited; 1, alert; 2, sedated; 3, drowsy; 4, no response to verbal command. The pain score was assessed immediately after tracheal extubation using the following score: 0, no pain; 1, slight (no analgesic required); 2, moderate (analgesic provided on request); and 3, severe (grimacing and complaining of pain). The time from the discontinuation of nitrous oxide until response to verbal command (time to response) and until extubation (time to extubation) were recorded. Arterial partial pressure of carbon dioxide was measured at pre-induction and post-extubation periods. The dose of analgesics during postoperative 24-h period was recorded.

Values were expressed as mean ± standard error. Intergroup comparison of demographics, hemodynamic variables, time to response, time to extubation, and $Paco_2$ values were carried out using unpaired Student's *t*-test. Scores of sedation and pain, and requirement of analgesics were compared using the unpaired Wilcoxon test. Incidences of patients needing vasodilators were compared using chi-square analysis. Statistical comparisons within groups were tested using analysis of variance for repeated measures followed by the Bonferroni inequality correction for *t*-test. A value of $P < 0.05$ was used as the criteria for statistical significance.

Results

There were no significant differences between the two groups with respects to sex distribution, weight, age, associated disease, and type and duration of surgery (Table 1). Hemodynamic data are shown in Tables 2 and 3. Both arterial blood pressure and heart rate increased with tracheal intubation and skin incision in both groups. The increase of heart rate by tracheal intubation was greater in the diazepam group than in the clonidine group. Heart rate in the recovery room was lower than that prior to preanesthetic in the clonidine group, while no significant difference was shown between groups. The requirement of vasodilators was different between two groups: only one patient in the clonidine group and seven patients in the diazepam group ($P < 0.05$, Table 4). The time to response or to extubation was not different between the two groups (Table 4). The sedation score both on arrival in the operating room and at emergence was not different between the groups (Table 4). The pain score of the diazepam group (1.5 ± 0.2) was higher than that in the clonidine group (0.6 ± 0.2, $P < 0.05$). The requirement of analgesics during the postoperative 24-h period in the clonidine group (1.0 ± 0.2) was lower than that in the diazepam group (2.0 ± 0.3, $P < 0.05$).

Discussion

Clonidine reduced the requirement of vasodilators during the operative period. It also promoted smooth emergence from sevoflurane anesthesia by reducing the pain score and the postoperative requirement for analgesics, and by maintaining sedated state without affecting the fast recovery, which is one of the advantages of sevoflurane anesthesia.

Table 1. Demographics of patients

Group	Diazepam (n = 11)	Clonidine (n = 11)	P
Age (years)[a]	52.0 ± 2.1	52.7 ± 2.4	n.s.
Sex (male/female)	8/3	9/2	n.s.
Weight (kg)[a]	162.3 ± 2.6	162.1 ± 2.7	n.s.
Type of surgery			
Cholecystectomy	7	7	n.s.
Gastrectomy	4	4	n.s.
Duration of surgery (min)[a]	141 ± 22	103 ± 14	n.s.
Number of patients with associated disease			
Hypertension	2	3	n.s.
Diabetes mellitus	2	2	n.s.

n.s., not significant.
[a] Data are expressed as mean ± SEM.

Table 2. Blood pressure changes in both groups

Group	Systolic (mmHg) Diazepam (n = 11)	Systolic (mmHg) Clonidine (n =11)	P	Diastolic (mmHg) Diazepam (n = 11)	Diastolic (mmHg) Clonidine (n = 11)	P
In the ward[a]	116 ± 4	116 ± 4	n.s.	72 ± 3	73 ± 4	n.s.
Pre-induction	124 ± 5	119 ± 5	n.s.	74 ± 4	71 ± 4	n.s.
Post-induction	107 ± 6	109 ± 3	n.s.	65 ± 4	67 ± 3	n.s.
Post-intubation	171 ± 9*	149 ± 10*	n.s.	99 ± 5*	94 ± 7*	n.s.
Pre-incision	110 ± 5	100 ± 4	n.s.	67 ± 5	62 ± 2	n.s.
After incision						
5 min	146 ± 7*	149 ± 8*	n.s.	94 ± 6*	91 ± 4*	n.s.
10 min	168 ± 7*	142 ± 4*	n.s.	102 ± 3*	85 ± 3	n.s.
In the recovery	136 ± 7	136 ± 7	n.s.	79 ± 4	79 ± 6	n.s.

All data are expressed as mean ± SEM.
n.s., not significant.
* $P < 0.05$ versus value in the ward.
[a] Prior to administration of preanesthetic.

Table 3. Heart rate changes in both groups

Group	Diazepam (bpm) (n = 11)	Clonidine (bpm) (n = 11)	P
In the ward	77.9 ± 5.1	71.3 ± 3.7	n.s.
Pre-induction	86.0 ± 4.6	74.5 ± 5.3	n.s.
Post-induction	87.9 ± 3.8	75.8 ± 5.3	n.s.
Post-intubation	101.2 ± 3.6*	87.7 ± 5.0*	<0.05
Pre-incision	81.6 ± 4.1	70.1 ± 4.7	n.s.
After incision			
5 min	85.6 ± 3.5	80.4 ± 4.6	n.s.
10 min	91.9 ± 5.1*	80.4 ± 3.8	n.s.
In the recovery	67.6 ± 2.7	60.1 ± 3.1*	n.s.

n.s., not significant.
* $P < 0.05$ versus value in the ward.

Clonidine, in the present study, did not demonstrate sedative or hemodynamic effects on arrival in the operating room. It is controversial whether patients who receive clonidine are sedated [8,11,12] or not [10] on arrival in the operating room. Clonidine has been reported to decrease blood pressure in hypertensive or elderly patients [8,11], while less effect is evident in normotensive patients [13] such as in the present study. Patients in the present study received a nasogastric tube and a Foley catheter in the ward. These maneuvers might attenuate the sedative and hemodynamic effects of clonidine, if any, in the pre-induction period.

Arterial blood pressure and heart rate increased in both groups with laryngoscopy and tracheal intubation, but the increase in heart rate in the clonidine-pretreated group was less than that in the diazepam-pretreated group. This suppressive action of clonidine on intubation-associated cardiovascular responses is in accordance with the results of other investigators [7–11].

In the present study, average arterial blood pressure increased with skin incision and surgical manipulation from 110/67 mmHg to 168/102 mmHg 10 min following skin incision in the diazepam group and vasodilators were required during operation in 7 of 11 patients. We previously studied the action of sevoflurane on the somatosensory evoked potential and spontaneous brain activity in the cat [6]. Although sevoflurane depressed spontaneous brain activity, it augmented the somatosensory evoked potential, suggesting a weak suppressive action of sevoflurane on CNS response to peripheral stimulation while tonic CNS activity was suppressed. Murakawa et al. [15] measured plasma catecholamines during abdominal surgery with sevoflurane anesthesia, and reported that the elevations in plasma epinephrine and norepinephrine induced by surgical manipulation were not inhibited by sevoflurane.

Table 4. Effects of preanesthetic medication on variables in anesthetic courses in sevoflurane anesthesia

Group	Diazepam	Clonidine	P
Number of patients needed vasodilators	7	1	<0.05
Sedation score[a]			
On arrival at op. room	1.4 ± 0.2	1.3 ± 0.1	n.s.
At emergence	1.7 ± 0.2	2.0 ± 0	n.s.
Pain score[a]	1.5 ± 0.2	0.6 ± 0.2	<0.05
Number of requirement of analgesics	2.0 ± 0.3	1.0 ± 0.2	<0.05
Time to response (min)	2.9 ± 0.8	3.0 ± 0.9	n.s.
Time to extubation (min)	7.2 ± 1.0	5.9 ± 1.1	n.s.
$Paco_2$ (mmHg)			
Pre-induction	41.4 ± 0.7	41.7 ± 1.0	n.s.
Post-extubation	37.7 ± 3.8	43.2 ± 1.7	n.s.

n.s., not significant.
[a] Expressed as mean ± SEM.

Other factors suspected in regard to the hypertensive response in the diazepam group were the low concentration of sevoflurane and the small dose of supplemental fentanyl. In comparison with the diazepam group, hemodynamics in patients in the clonidine group were more stable. The suppressive actions of clonidine on hemodynamic and catecholamine responses to surgical manipulation have been reported by several investigators [7–14]. The present study confirmed the more stable hemodynamics during sevoflurane anesthesia with clonidine premedication.

Heart rate in the recovery room was lower than that in the ward in the clonidine group. The bradycardia in the recovery room in patients pretreated with clonidine is in agreement with a report of Orko et al. [9]. Another factor responsible for bradycardia in the present study might be reversal of pancuronium. Pancuronium has an anticholinesterase action, and reversal of muscle relaxation by inhibition of cholinesterase often induces bradycardia [16–18]. Clonidine would potentiate this bradycardia response.

The sedative and analgesic actions of clonidine seemed to promote smooth recovery from sevoflurane anesthesia. The peak plasma level of clonidine was reported at 2.5 h after oral administration [19]. The average duration of surgery in this study was 2 h, and clonidine should be effective in the immediate postoperative period. Ghignone et al. [11] also revealed the sedative action of clonidine premedication on arrival in the recovery room. Although sedative states were demonstrated in all patients at recovery from anesthesia, times to response and to extubation were not prolonged, and hence the sedative effect of clonidine did not prolong the fast recovery from sevoflurane anesthesia.

We administered fentanyl as a supplement to sevoflurane anesthesia in both groups. The supplement with analgesics is required due to the weak suppressive action of sevoflurane on CNS response to surgical manipulation. If no analgesic such as fentanyl was administered, differences between the two groups in cardiovascular variables during anesthesia, and postoperative pain and sedation scores would be revealed more clearly, because diazepam had no analgesic action.

In conclusion, clonidine premedication, because of its cardiovascular action, its sedative and analgesic actions, and its beneficial effect on recovery state, appears to be well suited for sevoflurane anesthesia in upper abdominal surgery.

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