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ORIGINAL ARTICLE

Concomitant administration of nitrous oxide and remifentanil reduces oral tissue blood flow without decreasing blood pressure during sevoflurane anesthesia in rabbits

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Abstract
Purpose To determine whether continuous administration of nitrous oxide and remifentanil—either alone or together—alters blood flow in oral tissues during sevoflurane anesthesia.
Methods Eight male tracheotomized Japanese white rabbits were anesthetized with sevoflurane under mechanical ventilation. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), common carotid arterial blood flow (CCBF), tongue mucosal blood flow (TMBF), mandibular bone marrow blood flow (BBF), masseter muscle blood flow (MBF), upper alveolar tissue blood flow (UBF), and lower alveolar tissue blood flow (LBF) were recorded in the absence of all test agents and after administration of the test agents (50 % nitrous oxide, 0.4 μg/kg/min remifentanil, and their combination) for 20 min.
Results Nitrous oxide increased SBP, DBP, MAP, CCBF, BBF, MBF, UBF, and LBF relative to baseline values but did not affect HR or TMBF. Remifentanil decreased all hemodynamic variables except DBP. Combined administration of nitrous oxide and remifentanil recovered SBP, DBP, MAP, and CCBF to baseline levels, but HR and oral tissue blood flow remained lower than control values.
Conclusions Our findings suggest that concomitant administration of nitrous oxide and remifentanil reduces blood flow in oral tissues without decreasing blood pressure during sevoflurane anesthesia in rabbits.

Keywords Oral tissue blood flow · Nitrous oxide · Remifentanil · Sevoflurane

Introduction

Limiting bleeding from the oral tissues, including bone marrow and muscle, is especially important in oral and maxillofacial surgery such as orthognathic surgery and oral cancer resection. Because of the abundant blood vessels in the oral mucosa and jaw bone [1], many methods, including induced hypotension, have been described for controlling the blood flow in oral tissues during general anesthesia [2–4]. However, safer strategies to control oral tissue blood flow have been sought because of reports of complications from induced hypotension [5, 6]. Remifentanil decreases blood flow in oral tissues, including the mandibular bone marrow, without markedly reducing the mean arterial pressure during propofol or sevoflurane anesthesia [7, 8]. In addition, neither rocuronium nor vecuronium, which are frequently used during anesthesia to provide muscle relaxation, affects blood flow in the mandibular bone marrow or masseter muscle during sevoflurane anesthesia [9]. Taken together, these studies suggest that remifentanil may be useful and safe for decreasing oral tissue blood flow during anesthesia provided by sevoflurane combined with rocuronium or vecuronium.

Nitrous oxide, which has an analgesic action [10], easily maintains stable hemodynamics when provided with volatile anesthetics during oral and maxillofacial surgery. Nitrous oxide did not increase tongue mucosal tissue blood flow during isoflurane anesthesia at 0.5 minimum

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alveolar concentration [11]. Because no other studies have addressed the combined effects of nitrous oxide and general anesthetics on oral tissue blood flow (including that in the bone marrow and muscle), we examined these effects in rabbits under sevoflurane anesthesia. In addition, we assessed the use of concomitant administration of nitrous oxide and remifentanil to minimize oral tissue blood flow during oral and maxillofacial surgery.

Materials and methods

Animals

This study was registered with The Animal Research Ethics Committee at Tokyo Dental College (permit no. 252501). All animals received humane care in accordance with the guidelines for the treatment of experimental animals, as approved by Tokyo Dental College. Male Japanese white rabbits ($n = 8$; weight approximately 2.5 kg; Sankyo Labo, Tokyo, Japan) received rabbit chow and water ad libitum.

Anesthesia and animal preparations

During surgical preparations, rabbits were anesthetized with isoflurane (3.0 % in oxygen; Forane®, Abbott Japan, Tokyo, Japan) by using a vaporizer. The rectal temperature was maintained at 39.0 °C–39.5 °C throughout the study. Before we performed the necessary skin incisions for each of the preparatory procedures in rabbits, we injected appropriate doses of 1 % lidocaine solution (Xylocaine®; AstraZeneca, Osaka, Japan) into the surgical field. A 20-French non-cuffed pediatric tracheal tube was inserted into the trachea through a tracheostomy. The left posterior auricular marginal vein and right femoral artery were cannulated with 22- and 20-gauge Teflon indwelling catheters, respectively. Rabbits received acetated Ringer's solution containing 1 % glucose (10 mL/kg/h intravenously; Physio 140 Injection®, Otsuka Pharmaceutical, Tokyo, Japan); muscle relaxation was then achieved by adding rocuronium bromide (14 μg/kg/min; Eslax®, Schering-Plough, Tokyo, Japan). The lungs were ventilated mechanically to maintain an end-tidal partial pressure of carbon dioxide of 35–40 mmHg, which was monitored continuously with an anesthetic gas monitor (Capnomac®; Datex, Helsinki, Finland). Femoral arterial blood pressure was recorded continuously with a pressure transducer (model P231D; Gould, Oxnard, CA, USA), and heart rate was determined by counting pressure pulse waves. The flow probe (type 3SB; Transonic, Ithaca, NY, USA) of an ultrasound flowmeter (model TS420; Transonic) was placed at the isolated left common carotid artery to measure common carotid arterial blood flow. Tongue mucosal blood flow was measured with a laser Doppler flowmeter (model ALF21; Advance, Tokyo, Japan); a contact-type probe (type C; Advance) was placed at the anterior third of the left dorsal surface of the tongue. To measure blood flow in the mandibular bone marrow and masseter muscle, an incision was made along the left inferior margin of the mandible without local anesthesia to prevent a lidocaine-induced change in tissue blood flow. The exposed periosteum of the mandibular body was then detached to expose the surface of the mandibular body. A round burr (ISO 008; Morita, Saitama, Japan) was used to drill a small (diameter, approximately 1 mm) hole through the cortical bone and into the bone marrow. The needle probe of a hydrogen clearance tissue blood flowmeter (UHE-100; Unique Medical, Tokyo, Japan) was inserted into the mandibular bone marrow, left masseter muscle, left upper alveolar tissue, and left lower alveolar tissue.

After these preparatory surgeries were completed, isoflurane was replaced with sevoflurane (Sevofrane®; Maruishi Pharmaceutical, Osaka, Japan) for inhalational anesthesia. Sevoflurane was administered to maintain an end-tidal concentration of 1.8 %. Baseline measurements were obtained at least 60 min after completion of the surgical preparations, when hemodynamic and respiratory parameters had stabilized. Systolic, diastolic, and mean arterial blood pressure; heart rate; and blood flow in the common carotid artery and tongue mucosal tissue were recorded continuously by using a polygraph (series 360; NEC Sanei, Tokyo, Japan). In addition, blood flow in the mandibular bone marrow, masseter muscle, and upper and lower alveolar tissue was analyzed by using a data collection and analysis system (model UCO; Unique Medical, Tokyo, Japan).

Study protocol

After baseline data were obtained, 50 % nitrous oxide was administered for 20 min, after which hemodynamic parameters and oral tissue blood flow were re-evaluated. A washout period of at least 20 min was provided, after which remifentanil (Ultiva®; Janssen Pharmaceutical, Tokyo, Japan) was infused at a rate of 0.4 μg/kg/min; measurements were obtained after 20 min. We then added 50 % nitrous oxide during remifentanil infusion for 20 min, after which the parameters were measured once more. Administration of remifentanil and nitrous oxide were stopped after all assessments were made. Hemodynamic parameters were confirmed to have returned to baseline no less than 30 min after discontinuation of the experimental drugs.

According to previous studies, we set the concentration of sevoflurane to 1.8 % [7, 8, 12], which is equal to 0.5 minimum alveolar concentration for rabbits [13, 14]; the concentration of nitrous oxide to 50 % [11]; the infusion rate of remifentanil to 0.4 μg/kg/min (which previously significantly decreased tissue blood flow without

Table 1 Hemodynamic parameters and tissue blood flow in rabbits anesthetized with sevoflurane

	Baseline	Nitrous oxide	Remifentanil	Remifentanil + nitrous oxide	Recovery
HR (beats per min)	320.8 ± 21.4	323.0 ± 12.3	247.6 ± 27.3*	246.0 ± 25.6*	311.1 ± 22.3#
SBP (mmHg)	128.3 ± 22.5	142.5 ± 14.4*	110.8 ± 15.1*	121.1 ± 13.5#	134.8 ± 16.7#
DBP (mmHg)	63.3 ± 13.8	73.8 ± 12.1*	59.5 ± 12.6	69.4 ± 12.0#	68.6 ± 13.1#
MAP (mmHg)	86.5 ± 13.7	99.0 ± 9.8*	76.1 ± 12.2*	86.0 ± 12.3#	92.1 ± 11.4#
CCBF (mL/min)	42.8 ± 14.3	49.6 ± 17.6*	34.5 ± 12.4*	41.9 ± 13.7#	46.1 ± 15.9#
TMBF (mL/min/100 g)	29.8 ± 4.0	31.8 ± 4.9	21.8 ± 6.9*	22.6 ± 7.7*	27.6 ± 7.0#
BBF (mL/min/100 g)	31.9 ± 3.8	41.2 ± 2.0*	21.1 ± 3.0*	26.0 ± 2.8*,#	31.9 ± 4.8#
MBF (mL/min/100 g)	34.3 ± 4.2	39.2 ± 6.3*	22.6 ± 5.6*	27.1 ± 6.0*,#	32.2 ± 4.5#
UBF (mL/min/100 g)	31.0 ± 4.0	38.4 ± 6.5*	21.8 ± 5.8*	24.3 ± 4.4*	28.8 ± 4.1#
LBF (mL/min/100 g)	32.5 ± 5.4	39.1 ± 9.4*	19.2 ± 4.1*	24.0 ± 4.2*,#	33.0 ± 4.4#

Data are presented as mean ± standard deviation ($n = 8$)

HR heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *CCBF* common carotid arterial blood flow, *TMBF* tongue mucosal blood flow, *BBF* mandibular bone marrow blood flow, *MBF* masseter muscle blood flow, *UBF* upper alveolar tissue blood flow, *LBF* lower alveolar tissue blood flow

* $P < 0.05$ compared with baseline

# $P < 0.05$ compared with remifentanil

substantial changes in blood pressure [8]); and the rate of infusion of rocuronium bromide to 14 μg/kg/min [9].

Statistical analysis

All data are presented as mean ± standard deviation. For intragroup comparisons, one-way analysis of variance for repeated measures was followed by the Student–Newman–Keuls test. *P* values less than 0.05 were considered statistically significant.

Results

Adding nitrous oxide to sevoflurane anesthesia in rabbits increased systolic, diastolic, and mean arterial blood pressures (Table 1), consequently significantly ($P < 0.05$) increasing blood flow in the common carotid artery (approximately 16.1 % increase compared with baseline value), mandibular bone marrow (30.9 %), masseter muscle (14.1 %), and upper (24.5 %) and lower (19.8 %) alveolar tissue but not in the tongue mucosal tissue (Fig. 1).

Adding remifentanil alone to sevoflurane anesthesia in rabbits decreased all measured hemodynamic and tissue blood flow parameters except diastolic blood pressure (Table 1). In addition, blood flow in all oral tissues decreased significantly ($P < 0.05$) relative to control values (common carotid, decrease of 19.3 %; tongue mucosal tissue, 27.3 %; mandibular bone marrow, 33.1 %; masseter muscle, 34.0 %, upper alveolar tissue, 30.6 %; and lower alveolar tissue, 40.8 %) (Fig. 1).

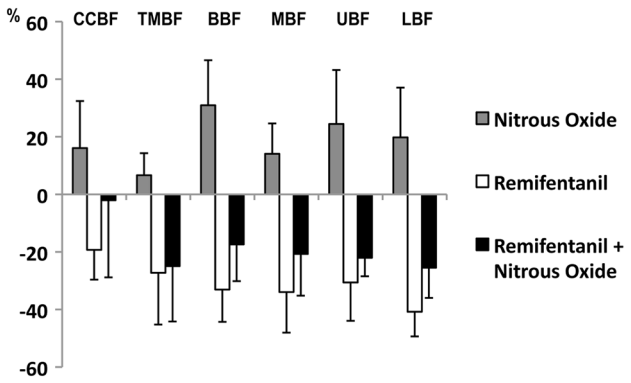

Fig. 1 Changes in oral tissue blood flow. Adding nitrous oxide to sevoflurane anesthesia increased ($P < 0.05$) common carotid artery blood flow (*CCBF*), mandibular bone marrow blood flow (*BBF*), masseter muscle blood flow (*MBF*), upper alveolar tissue blood flow (*UBF*), and lower alveolar tissue blood flow (*LBF*) but not tongue mucosal blood flow (*TMBF*) relative to baseline values in rabbits. Infusion of remifentanil alone during sevoflurane anesthesia led to decreases in CCBF, TMBF, BBF, MBF, UBF, and LBF, whereas concomitant administration of nitrous oxide and remifentanil during sevoflurane anesthesia supported the return of CCBF alone to control values; other parameters of oral tissue blood flow remained lower than baseline values. Data (mean ± standard deviation; $n = 8$) are expressed as percentages of baseline values

Adding nitrous oxide to remifentanil during sevoflurane anesthesia caused recovery of the systolic, diastolic, and mean arterial blood pressures to control values. Although adding nitrous oxide to remifentanil significantly increased the common carotid artery blood flow and the oral tissue blood flow measures (except tongue mucosal blood flow

and upper alveolar tissue blood flow) from the values that were reduced by remifentanil, these oral blood flow measures remained depressed (Table 1; Fig. 1).

Discussion

The main finding of this study was that adding nitrous oxide did not cause the recovery of oral tissue blood flow, which was decreased by administration of remifentanil, to control levels during sevoflurane anesthesia in rabbits.

Nitrous oxide, which augments sympathetic nervous activity [15–18], increased blood flow in all oral tissues monitored except the tongue mucosa during sevoflurane anesthesia; the data regarding tongue mucosal blood flow agree with those reported previously [11]. Because no other studies have addressed the combined effect of nitrous oxide and general anesthetics on oral tissue blood flow (except tongue mucosal blood flow), our current study provides new knowledge in this regard in the context of sevoflurane anesthesia. In contrast to the effect of nitrous oxide and in agreement with previous findings [8], remifentanil decreased all hemodynamic and tissue blood flow measures in sevoflurane-anesthetized rabbits except diastolic blood pressure. Adding nitrous oxide during remifentanil infusion returned blood pressure parameters and common carotid blood flow to baseline levels; however, oral tissue blood flow and heart rate remained below control values. In other words, concomitant administration of nitrous oxide and remifentanil decreased oral tissue blood flow without a concomitant reduction in blood pressure.

Well-known adverse effects of remifentanil include bradycardia and hypotension resulting from the drug's vagotonic and sympatholytic actions as a specific μ-receptor agonist [19]. Hence, the effects of remifentanil include a dose-dependent decrease in heart rate and arterial pressure [20]. In animal experiments, remifentanil decreases blood pressure in an infusion-rate-dependent manner, with a significant reduction in oral tissue blood flow during sevoflurane or propofol anesthesia [8]. In humans, remifentanil at dosages greater than 0.3 μg/kg/min can induce profound bradycardia and hypotension [21, 22]; in rabbits, mean arterial pressure decreased slightly and oral tissue blood flow decreased markedly at a remifentanil infusion rate of 0.2 μg/kg/min [8]. Taken together, these findings suggest that an appropriate infusion rate of remifentanil for reducing oral tissue blood flow without deleterious decreases in heart rate and blood pressure is approximately 0.2 μg/kg/min.

Investigating the mechanism underlying the reduction in oral tissue blood flow and maintenance of blood pressure due to concomitant administration of nitrous oxide and remifentanil was beyond the scope of our study. However, in a previous study [12], remifentanil infusion during sevoflurane anesthesia in rabbits led to decreases in heart rate, systolic blood pressure, and blood flow in the common carotid artery and oral tissues. Administration of naloxone (a μ-receptor antagonist) reversed the remifentanil-induced effects [12]. This finding suggests that the remifentanil-associated decrease in tissue blood flow that we found here is a μ-receptor-mediated phenomenon. In contrast, when the α-receptor antagonist phentolamine was administered in the cited study [12], blood flow in the oral tissues—but not heart rate, systolic blood pressure, or carotid arterial blood flow—returned to control levels, suggesting a redistribution of blood flow in the head and neck region through peripheral vasodilatory mechanisms. Furthermore, there is a question whether the autoregulation of cerebral blood flow is maintained during remifentanil infusion, because remifentanil reduced the common carotid artery blood flow. Additional research is needed to clarify the mechanisms underlying these various effects.

For safe and effective anesthesia during oral and maxillofacial surgery, we should address both the reduction in oral tissue blood flow and the maintenance of systemic blood pressure. In our current study, nitrous oxide successfully maintained blood pressure whereas remifentanil effectively reduced blood flow in oral tissues. Therefore, concomitant administration of nitrous oxide and remifentanil safely decreases oral tissue blood flow during sevoflurane anesthesia for maxillofacial surgery in rabbits. Additional studies are needed to assess the use of nitrous oxide with another anesthetic (e.g., propofol) to minimize the postoperative nausea and vomiting that can accompany the use of nitrous oxide with volatile anesthetics [23] in humans to achieve safe anesthesia for oral and maxillofacial surgery.

In conclusion, our results suggest that concomitant administration of nitrous oxide and remifentanil might reduce oral tissue blood flow without decreasing blood pressure during sevoflurane anesthesia for maxillofacial surgery.

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