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Rocuronium and vecuronium do not affect mandibular bone marrow and masseter muscular blood flow in the rabbit

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Abstract

**Purpose:** The goal of this study was to investigate the effect of rocuronium and vecuronium continuous infusion on oral tissue blood flow in the rabbit.

**Materials and Method:** We utilized eight male Japan White rabbits. The infusion rate of rocuronium (Group R) was 7 mcg/kg/min (R-7), 14 mcg/kg/min (R-14) and 28 mcg/kg/min (R-28) for 20 minutes in this order. After rocuronium was discontinued and confirmed the body movement, continuous infusion of vecuronium was started. The infusion rate of vecuronium was 1.6 mcg/kg/min (V-1.6), 3.2 mcg/kg/min (V-3.2) and 6.4 mcg/kg/min (V-6.4) for 20 minutes in this order. Observed variables were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), common carotid artery blood flow (CCBF), tongue mucosal blood flow (TMBF), oxygen partial pressure of the mandibular bone marrow (PbO₂) and oxygen partial pressure of the masseter muscle (PmO₂).

**Results:** HR in both groups tended to decrease depending on the infusion rate. CCBF in Group R was increased depending on the infusion rate. TMBF in Group V was decreased depending on the infusion rate. There were no differences in DBP, MAP, PbO₂ and PmO₂.
between two groups. SBP in both groups showed no major change.

**Conclusion:** Rocuronium and vecuronium did not change mandibular bone marrow and masseter muscular blood flows. Vecuronium decreased TMBF depending on the infusion rate.
In oral and maxillofacial surgery, especially in orthognathic surgery, control of bleeding from bone marrow has an important influence on performing smooth surgery. Consequently, several studies about control of oral tissue blood flow during anesthesia have been conducted.

A common method for minimizing bleeding during surgery is deliberate hypotension. There are some reports focusing on the control of oral tissue blood flow during deliberate hypotension. However, deliberate hypotension sometimes has critical complications such as ischemia of vital organs, delayed emergence, postoperative bleeding, and severe organ damages. Therefore, other methods for controlling oral tissue blood flow has been studied.

Tongue mucosal blood flow (TMBF) was decreased during fentanyl and propofol administration in the rabbit. Mandibular bone marrow blood flow was decreased during infusion of remifentanil under propofol and sevoflurane anesthesia in the rabbit. Mandibular bone marrow blood flow was also decreased under hypocapnia due to hyperventilation in the rabbit. These results suggest the possibility of a new oral tissue blood flow control method by utilizing anesthetic agents or anesthesia management.
techniques without a major change of blood pressure as deliberate hypotension.

Nondepolarizing muscle relaxants are frequently used during general anesthesia. Several studies reported the effects of nondepolarizing muscle relaxants on hemodynamic variables and organ tissue blood flow. Cerebral blood flow was decreased after d-tubocurarine administration, whereas cerebral and skin blood flow were increased after vecuronium administration. Although nondepolarizing muscle relaxants are also frequently used during general anesthesia in oral and maxillofacial surgery, the effects of nondepolarizing muscle relaxants on oral tissue blood flow remains unknown. If nondepolarizing muscle relaxants increase oral tissue blood flow, attention should be paid during oral and maxillofacial surgery including orthognathic surgery.

In this study, therefore, we investigated the effect of rocuronium and vecuronium continuous infusion on oral tissue blood flow. Targeted variables included TMBF, oxygen partial pressure of the mandibular bone marrow (PbO₂) and oxygen partial pressure of the masseter muscle (PmO₂).
Materials and methods

We utilized eight male Japan White rabbits (2.2-2.7kg). Rabbits were purchased from Sankyo Labo Company, Tokyo. This study was performed according to “The Guidelines for the Treatment of Experimental Animals in Tokyo Dental College”. All animals were allowed food and water *ad libitum* until the morning of the experiment.

Anesthesia was induced by inhalation of 4.0% isoflurane in oxygen delivered via a mask. Before skin incisions were made for tracheostomy and femoral artery cannulation, 0.3 ml of 1% lidocaine without epinephrine was injected. A #20 Fr non-cuffed pediatric tracheal tube was inserted into the trachea through tracheostomy. The left auricular marginal vein and right femoral artery were cannulated with 22- and 20-gauge Teflon indwelling catheters, respectively. Femoral artery blood pressure was continuously monitored with a pressure transducer (P231D; Gould, Oxnard, California). Heart rate (HR) was recorded by a tachograph triggered by blood pressure wave. Common carotid blood flow (CCBF) was measured with an ultrasound flowmeter (T108; Transonic, Ithaca NY). A flow probe (type 3SB) was applied to the isolated left common carotid artery. TMBF was measured with a laser Doppler flowmeter (ALF21; Unique...
Medical, Tokyo). A contact-type probe (type C; Unique Medical) for TMBF measurement was placed at the anterior third of the left dorsal surface of the tongue. Care was taken to minimize the contact pressure of the probe to prevent blood flow disturbance in the tongue mucosa. HR, CCBF and TMBF are expressed as a percentage of control values.

After the skin incision along the left inferior margin of the mandible without local anesthesia, the periosteum of the mandibular body was exposed. The periosteum was detached to expose the surface of the mandibular body. A small hole (approximately 1 mm in diameter) perforating into the bone marrow through the cortical bone was drilled with a round bar (ISO. 008, Morita, Japan). In addition, after the skin incision along the right inferior margin of the mandible without local anesthesia, the fascia of the masseter muscle was detached to expose the masseter muscle. Two needle probes of a PO2 monitor (PO2-100DW, Unique Medical, Japan) were inserted into the bone marrow and the masseter muscle to measure PbO2 and PmO2, respectively.

After completion of experimental preparations, isoflurane inhalation was discontinued. Then inhalation of sevoflurane was started at 1.8% of end-tidal concentration and maintained at that level for more than 60 min to stabilize the animal’s
hemodynamic and respiratory parameters. After intravenous acetated Ringer’s solution was started at 10 ml/kg/hr, the animals were paralyzed with 7 mcg/kg/min rocuronium bromide (Eslax, Schering-Plough, Tokyo) and mechanically ventilated. End-tidal partial pressure of carbon dioxide (ETCO₂) was maintained at about 35mmHg. Sevoflurane concentration was continuously monitored with an anesthetic gas monitor (Capnmac; Datex, Helsinki). Body temperature was continuously monitored with a rectal probe and maintained between 39.0 and 39.5°C with the aid of a heating lamp.

The infusion rate of rocuronium (Group R) was 7 mcg/kg/min (R-7), 14 mcg/kg/min (R-14) and 28 mcg /kg/min (R-28) for 20 minutes in this order. After rocuronium was discontinued and confirmed the body movement, continuous infusion of vecuronium bromide (Group-V, Musculax, Schering-Plough, Tokyo) was started. The infusion rate of vecuronium was 1.6 mcg/kg/min (V-1.6), 3.2 mcg/kg/min (V-3.2) and 6.4 mcg/kg/min (V-6.4) for 20 minutes in this order.

The observed parameters were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), HR, CCBF, TMBF, PbO₂ and PmO₂. All of these variables were continuously recorded on a polygraph (Series360 NEC; Sanei,
Tokyo). All data were measured 15 minutes and 20 minutes after the start of continuous infusion of rocuronium or vecuronim. The mean of two values was calculated.

In this study, data are expressed as the mean ± standard deviation. A one-way analysis of variance for repeated measurements followed by the Student-Newman-Keuls test for multiple comparisons were used in this study. P-values less than 0.05 were considered statistically significant.
Results

There were no differences in DBP, MAP, PbO$_2$ and PmO$_2$ between Group R and Group V. SBP showed no major change in both groups. (Tables 1 and 2)

HR in Group R was larger than that in Group V. HR in both groups tended to decrease depending on the infusion rate. HR at R-28 was decreased by 6% in comparison with that at R-7. Similarly, HR at V-6.4 was decreased by 5% in comparison with that at V-1.6. (Fig. 1)

CCBF in Group R was increased depending on the infusion rate. CCBF at R-28 was increased by 24% in comparison with that at R-7. (Fig. 2) CCBF in Group V showed no change.

TMBF in Group R showed no change. TMBF in Group V was decreased depending on the infusion rate. TMBF at V-6.4 was decreased by 19% in comparison with that at V-1.6. (Fig. 3)
Discussion

This study showed that HR in both groups tended to decrease depending on the infusion rate. CCBF was increased during infusion of rocuronium. TMBF was decreased during infusion of vecuronium. PbO$_2$ and PmO$_2$ remained unchanged throughout the experiment.

In a previous study, minimum alveolar concentration (MAC) of sevoflurane is 1.5 to 1.8 times as high as that of isoflurane. Therefore, isoflurane was used for induction of anesthesia and experimental preparations in this study because isoflurane was able to induce anesthesia more smoothly than sevoflurane. Anesthesia was maintained with 1.8% sevoflurane. This concentration was equal to 0.5 minimum alveolar concentration (MAC) of sevoflurane in the rabbit. Sevoflurane has less sympatholytic effects than isoflurane and these effects occur at the level higher than 0.75 MAC of sevoflurane.

In our preliminary study, minimal infusion rate of rocuronium which provided stable muscular relaxation was 7 mcg/kg/min during inhalation of 1.8% sevoflurane. In addition, based on previous studies and the results of our preliminary study, minimal
infusion rate of vecuronium for similar condition was 1.6 mcg/kg/min.\textsuperscript{22,23} Therefore, these infusion rates were adopted in this study. The potency of rocuronium at bolus injection is one-sixth that of vecuronium.\textsuperscript{24} Although, the potency of rocuronium and vecuronium during continuous infusion remains unknown, the infusion rate of rocuronium in this study was four to five times as much as that of vecuronium. The potency rate during infusion in this study was approximately equal to that at bolus injection. Therefore, we hypothesized \(7\) mcg/kg/min rocuronium and \(1.6\) mcg/kg/min vecuronium induced similar muscular relaxation in the rabbits. In human, the minimal infusion rate of rocuronium is approximately \(3.5\) mcg/kg/min during sevoflurane anesthesia and \(7\) mcg/kg/min during propofol anesthesia.\textsuperscript{25} It is therefore suggested that the required infusion rate of rocuronium during propofol anesthesia may be twice as much as that during sevoflurane anesthesia. Meanwhile, as shown in this study, the infusion rate of rocuronium is approximately \(7\) mcg/kg/min during sevoflurane anesthesia in the rabbit. Therefore, we chose \(14\) mcg/kg/min for tentative propofol anesthesia and \(28\) mcg/kg/min which was twice as much as \(14\) mcg/kg/min. The infusion rates of vecuronium \(1.6\) mcg/kg/min, \(3.2\) mcg/kg/min and \(6.4\) mcg/kg/min were adopted because of the
equipotency with rocuronium.

Oxygen partial pressure of the masseter muscle and mandibular bone marrow were measured in this study. Changes in oxygen partial pressure should reflect the increase or decrease of tissue blood flow because the oxygen consumption of the masseter muscle and mandibular bone marrow are minimal and stable during muscular relaxation.

It is reported that tissue oxygen partial pressure was decreased during tissue ischemia. Therefore, we believe that PbO$_2$ and PmO$_2$ should be good indicators for the blood flow of mandibular bone marrow and the masseter muscle, respectively.

In a previous report, tissue blood flows in brain, kidney, skin, liver, intestine and adrenals were increased depending on the infusion rate after vecuronium administration. Although changes in CCBF are dependent on changes in the blood flow in both internal carotid artery (ICA) and external carotid artery (ECA), ICA blood flow should minimally change due to the autoregulatory mechanisms of cerebral blood flow. In contrast, ECA blood flow may change depending on the degree of activations of alpha- and beta-adrenergic receptors, which innervate blood vessels of skin and mucosa (alpha-adrenergic receptors dominant) and skeletal muscles (beta-adrenergic receptors dominant).
Bone marrow blood flow may change depending on blood pressure.

In Group V, TMBF was significantly decreased by 19% without blood pressure change, while CCBF remained unchanged throughout the experiment. In a previous report, cerebral blood flow was increased by 15% to 20% after vecuronium administration. Therefore, no change in CCBF in this study suggest that an increase in the cerebral blood flow might be cancelled at least in part by a decrease in the head and neck mucosal blood flow after vecuronium administration. TMBF reduction may be attributable to local blood flow-regulating mechanisms in the oral mucosa because vecuronium has no effect on alpha- and beta-adrenergic receptors. Similar TMBF reduction was reported during the administration of fentanyl and remifentanil. In contrast, CCBF was increased by 24% in Group R. The increase in CCBF may be attributable to an increase in cerebral blood flow that was not canceled by decrease in mucosal blood flow if rocuronium had similar effects on cerebral blood flow with vecuronium.

In this study, mandibular bone marrow blood flow, which may change depending on blood pressure, remained unchanged because blood pressure showed no major change in both groups. Skeletal muscle blood flow may change depending on the
degree of activation of beta-adrenergic receptors. Therefore, it was suggested that masseter muscular blood flow remained unchanged because rocuronium \(^{13}\) and vecuronium \(^{13,14}\) have no effects on alpha- and beta-adrenergic receptors.

It has been reported that nondepolarizing muscle relaxants show their hemodynamic effects mainly through histamine release and vagolytic effects. \(^{13-19}\) D-tubocurarine causes hypotension and blood flow reduction in ascending aortic, limbs and viscera due to the depressant action on myocardial muscles and histamine release. \(^{13,17,18}\) Pancuronium causes tachycardia due to sympathetic activation whereas it does not have histamine releasing effects. \(^{13,15}\) Limb blood flow is decreased whereas viscera blood flow is hardly changed. \(^{19}\) Rocuronium \(^{28}\) and vecuronium \(^{19}\) do not have histamine releasing effects. Rocuronium may induce tachycardia due to vagolytic effects, while vecuronium induces bradycardia because it has no vagolytic effects. \(^{29}\) The results of this study are consistent with previous reports.

Based on the previous studies and the results of this study, it is suggested that rocuronium and vecuronium do not have major effects on hemodynamics \(^{13,14}\) and oral tissue blood flow during oral and maxillofacial surgery. Because rocuronium has a shorter
duration of action than vecuronium \textsuperscript{29} and is able to be administered by continuous infusion \textsuperscript{30}, rocuronium may be useful for oral and maxillofacial surgery.

The major flaw of this study was the lack of the control data without muscle relaxants. In a previous study, vecuronium did not affect systemic and regional hemodynamics.\textsuperscript{19} In our preliminary study, when TMBF, PbO\textsubscript{2} and PmO\textsubscript{2} were observed under 1 MAC of sevoflurane, tissue blood flow were not changed by an administration of 7 mcg/kg/min rocuronium or 1.6 mcg/kg/min vecuronium. However, because sympatholytic effects of sevoflurane occur at the level higher than 0.75 MAC,\textsuperscript{21} deep sevoflurane anesthesia in itself may affect tissue blood flow. Consequently, anesthesia was maintained under light anesthesia with 0.5 MAC of sevoflurane throughout the experiment. In this condition, the lung was frequently fighting against a ventilator without muscle relaxation. In addition, hemodynamic variables and tissue blood flow were unstable. Based on these results, in this study, the minimal rate of nondepolarizing muscle relaxants, 7mcg/kg/min for rocuronium and 1.6mcg/kg/min for vecuronium, were served as control.

In this study, the order of rocuronium and vecuronium was not randomized. In
our preliminary study, spontaneous breathing and gross body movement were observed few minutes after the cessation of rocuronium infusion. In a previous study, train of four ratio (TOFR) was reported 80 to 90% when head\textsuperscript{30,31} and leg\textsuperscript{31} could be continuously lifted for 5 sec in human. When TOFR is more than 80 to 90%, the residual effect of nondepolarizing muscle relaxants is negligible.\textsuperscript{31} In this study, therefore, we considered that muscle relaxant action of rocuronium almost disappeared when spontaneous breathing and gross body movement were confirmed. In contrast, vecuronium has a longer duration of action than rocuronium.\textsuperscript{24} In our preliminary study, it took more than 30 min until spontaneous breathing and gross body movement were recovered after continuous infusion of vecuronium 1.6 mcg/kg/min was discontinued. Therefore, rocuronium and vecuronium were administered in this order and not randomized in this study.

In conclusion, rocuronium and vecuronium did not change mandibular bone marrow and masseter muscular blood flows. Vecuronium decreased TMBF depending on the infusion rate.
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combined with balanced anaesthesia on haemodynamics and myocardial oxygen

metabolism in patients with ischemic heart disease during high-dose fentanyl anesthesia.

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Table 1  Hemodynamic variables, CCBF, TMBF, PbO₂ and PmO₂ in the rocuronium group

<table>
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<th>R-7</th>
<th>R-14</th>
<th>R-28</th>
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<tr>
<td>HR (bpm)</td>
<td>302.5±17.5</td>
<td>294.7±17.2</td>
<td>285.3±16.9</td>
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<tr>
<td>SBP (mmHg)</td>
<td>130.3±11.1</td>
<td>126.8±8.2</td>
<td>131.6±7.7</td>
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<tr>
<td>DBP (mmHg)</td>
<td>47.3±5.2</td>
<td>46.9±2.6</td>
<td>46.6±4.2</td>
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<tr>
<td>MAP (mmHg)</td>
<td>77.7±6.5</td>
<td>75.8±5.2</td>
<td>76.9±5.1</td>
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<tr>
<td>CCBF (ml/min)</td>
<td>26.1±7.3</td>
<td>28.4±7.5</td>
<td>32.4±9.8*</td>
</tr>
<tr>
<td>TMBF (ml/min/100g)</td>
<td>25.4±2.9</td>
<td>24.4±3.3</td>
<td>24.7±5.9</td>
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<tr>
<td>PbO₂ (mmHg)</td>
<td>38.4±9.7</td>
<td>37.9±13.0</td>
<td>37.3±14.2</td>
</tr>
<tr>
<td>PmO₂ (mmHg)</td>
<td>27.5±9.1</td>
<td>28.3±12.9</td>
<td>31.3±14.7</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; CCBF: common carotid artery blood flow; TMBF: tongue mucosal blood flow; PbO₂: oxygen partial pressure of the mandibular bone marrow; PmO₂: oxygen partial pressure of the masseter muscle
R-7: 7 mcg/kg/min rocuronium infusion; R-14: 14 mcg/kg/min rocuronium infusion;

R-28: 28 mcg/kg/min rocuronium infusion

Data are expressed as mean ± standard deviation

*p<0.05 vs R-7
Table 2  Hemodynamic variables, CCBF, TMBF, PbO$_2$ and PmO$_2$ in the vecuronium group

<table>
<thead>
<tr>
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<th>V-1.6</th>
<th>V-3.2</th>
<th>V-6.4</th>
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<tr>
<td>HR (bpm)</td>
<td>278.8±24.3†</td>
<td>266.3±31.0†</td>
<td>264.4±30.9</td>
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<tr>
<td>SBP (mmHg)</td>
<td>132.3±8.8</td>
<td>132.0±9.1</td>
<td>126.9±9.3#</td>
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<tr>
<td>DBP (mmHg)</td>
<td>47.5±4.5</td>
<td>50.4±8.4</td>
<td>49.3±8.8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>78.7±5.3</td>
<td>78.3±5.3</td>
<td>76.6±6.9</td>
</tr>
<tr>
<td>CCBF (ml/min)</td>
<td>30.9±10.2†</td>
<td>29.6±11.0</td>
<td>29.1±12.0</td>
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<tr>
<td>TMBF (ml/min/100g)</td>
<td>22.9±5.0</td>
<td>20.9±5.3*†</td>
<td>18.6±5.8*#†</td>
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<tr>
<td>PbO$_2$ (mmHg)</td>
<td>35.8±13.1</td>
<td>35.7±13.4</td>
<td>32.6±12.6</td>
</tr>
<tr>
<td>PmO$_2$ (mmHg)</td>
<td>30.6±15.6</td>
<td>29.4±15.0</td>
<td>26.9±12.4</td>
</tr>
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</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; CCBF: common carotid artery blood flow; TMBF: tongue mucosal blood flow; PbO$_2$: oxygen partial pressure of the mandibular bone marrow; PmO$_2$: oxygen partial pressure of the masseter muscle.
V-1.6: 1.6 mcg/kg/min vecuronium infusion; V-3.2: 3.2 mcg/kg/min vecuronium infusion;
V-6.4: 6.4 mcg/kg/min vecuronium infusion

Date are expressed as mean ± standard deviation

*p<0.05 vs V-1.6
# p<0.05 vs V-3.2
† p<0.05 R-7 vs V-1.6, R-14 vs V-3.2, or R-28 vs V-6.4
Figure legend

Fig. 1  Changes in heart rate (HR) in the rocuronium group (Group R) and the vecuronium group (Group V). HR was expressed as the percentage of respective R-7 and V-1.6 values. HR in both groups tended to decrease depending on the infusion rate.

R-7:  7 mcg/kg/min rocuronium infusion; R-14: 14 mcg/kg/min rocuronium infusion;
R-28: 28 mcg/kg/min rocuronium infusion; V-1.6: 1.6 mcg/kg/min vecuronium infusion;
V-3.2: 3.2 mcg/kg/min vecuronium infusion; V-6.4: 6.4 mcg/kg/min vecuronium infusion

Fig. 2  Changes in common carotid blood flow (CCBF) in the rocuronium group (Group R) and the vecuronium group (Group V). CCBF was expressed as the percentage of respective R-7 and V-1.6 values. CCBF at R-28 was increased by 24% in comparison with that at R-7. Asterisk indicates significant difference (p<0.05). R-7, R-14, R-28, V-1.6, V-3.2 and V-6.4 are same as in Fig. 1.

Fig. 3  Changes in tongue mucosal blood flow (TMBF) in the rocuronium group (Group R) and the vecuronium group (Group V). TMBF was expressed as the percentage
of respective R-7 and V-1.6 values. TMBF at V-6.4 was decreased by 19% in comparison
with that at V-1.6. Asterisk indicates significant difference (p<0.05). R-7, R-14, R-28,
V-1.6, V-3.2 and V-6.4 are same as in Fig. 1.
Fig. 1
Fig. 2