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<th>A comparison of blood loss in remifentanil-based anesthesia with sevoflurane or isoflurane during orthognathic surgery</th>
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A comparison of blood loss in remifentanil-based anesthesia with sevoflurane or isoflurane during orthognathic surgery.

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Abstract

Purpose: Previous studies reported that remifentanil reduced oral tissue blood flow. The aim of this study was to compare blood loss in remifentanil-based anesthesia with sevoflurane or isoflurane, potent vasodilating volatile anesthetic, during orthognathic surgery.

Patients and Methods: sixty four consenting patients classified as ASA class I or II, aged between 16 years and 50 years, who were scheduled for orthognathic surgery, participated in this study. The patients enrolled were randomized to the sevoflurane group (Sevo group, n = 32) or the isoflurane group (Iso group, n = 32). Anesthesia was maintained using 3 L/min air, 1 L/min oxygen, and end-tidal concentrations of 1.4% sevoflurane or 0.9% isoflurane (0.8 MAC for both groups). Remifentanil was continuously intused at 0.05–0.5 µg/kg/min to maintain mean blood pressure (MBP) at 60–65 mmHg. In addition to intraoperative blood loss (mL/kg), systolic blood pressure (SBP), MBP, diastolic blood pressure (DBP), heart rate (HR), and bispectral index values were compared.

Results: Although no significant differences between two groups were observed between two groups in intraoperative HR, SBP, MBP, or DBP, coefficient of variation
in mean blood pressure (CVMBP) was significantly greater in the Iso group (11.2 ± 3.6%) compared with the Sevo group (9.6 ± 2.2%). Intraoperative blood loss tended to be higher in the Iso group (4.79 ± 3.22 mL/kg) than the Sevo group (4.00 ± 1.98 mL/kg), while there was no significant difference between the two groups.

Conclusion: In a comparison of intraoperative blood loss in remifentanil-based anesthesia with sevoflurane or isoflurane during orthognathic surgery, no difference was observed between the two groups.
Introduction

Oral and maxillofacial surgery, and particularly orthognathic surgery, is performed in areas of high blood flow including the oral mucosa and bone marrow. Blood loss during surgery can obstruct the visual field, prolong operating times, and increase the risk of a blood transfusion.\(^1, 2\) Blood loss needs to be controlled during surgery to ensure the operation proceeds smoothly, to avoid the risks with blood transfusion, and to reduce postoperative complications.\(^3\)

Volatile anesthetics like isoflurane and sevoflurane are now widely used in oral and maxillofacial surgery. Previous research in rabbits showed that isoflurane increased blood flow in the tongue mucosa.\(^4\) Another study showed that isoflurane increased blood flow more than sevoflurane in the mandibular bone marrow and other oral tissues in rabbits.\(^5\) Clinical research has shown that isoflurane increases blood flow in the oral mucosa\(^6\) and sevoflurane reduces microcirculation under the tongue.\(^7\)

Narcotic analgesics fentanyl and remifentanil are also widely used for pain relief during oral and maxillofacial surgery under general anesthesia. Recent research has shown that, like the volatile anesthetics, these narcotic analgesics also affect oral tissue blood flow. Research in rabbits showed that fentanyl reduced blood flow in the
oral mucosa, and other studies have suggested that remifentanil may be useful for oral and maxillofacial surgery because it reduces blood flow in the mandibular bone marrow without markedly reducing blood pressure. Clinical research has shown that compared with fentanyl, remifentanil reduces blood loss and allows intraoperative hypotension without serious adverse events.

One study reported that during nasal septal surgery without a concomitant use of remifentanil, blood loss was higher with isoflurane than with sevoflurane. There are few studies that compare blood loss during oral and maxillofacial surgery when remifentanil is used as an adjunct to inhalation anesthesia, and it is unclear what effects the combined use of isoflurane with strong vasodilating potency and remifentanil have on the blood loss. We conducted this study to test the hypothesis that when blood loss in remifentanil-based anesthesia with sevoflurane and that with isoflurane during orthognathic surgery are compared, blood loss would be higher in the latter case.
**Patients and methods**

This study was approved by the Tokyo Dental College Ethics Committee (approval number 541). We enrolled 64 patients classified as ASA class I or II, aged between 16 years and 50 years, who were scheduled for Le Fort I osteotomy and sagittal split ramus osteotomy of the mandible at the Chiba Hospital of Tokyo Dental College. Written informed consent was obtained from all patients or their guardians. Patients with severe heart disease, liver/kidney disease, or muscle disease were excluded from the study.

The patients enrolled were randomized before surgery to the sevoflurane group (Sevo group, n = 32) or the isoflurane group (Iso group, n = 32). After transfer into the operating room, the patients were laid in a horizontal position and venous access was secured using a 20 G catheter inserted into the forearm cephalic vein. Anesthesia was induced using 0.01 mg/kg atropine sulfate (up to 0.5 mg/kg), 2 µg/kg fentanyl citrate, and 2 mg/kg propofol. Muscle relaxation was achieved using 0.6 mg/kg rocuronium bromide before nasotracheal intubation was performed. Anesthesia was maintained using 3 L/min air, 1 L/min oxygen, and end-tidal concentrations of 1.4% sevoflurane or 0.9% isoflurane (0.8 MAC for both groups), while muscle
relaxation was achieved through continuous administration of 5 \( \mu g/kg/min \) rocuronium bromide. Remifentanil continuously infused at 0.05–0.5 \( \mu g/kg/min \) to maintain mean blood pressure (MBP) during anesthesia at 60–65 mmHg. One percent lidocaine solution with 1:100,000 epinephrine was administered to the surgical field. The end-tidal carbon dioxide concentration was maintained during anesthesia in both groups at 35–45 mmHg through controlled mechanical ventilation. Acetated Ringer’s solution was administered at 8 mL/kg/h for fluid infusion during surgery. Continuous monitoring under anesthesia involved pulse oximetry, non-invasive blood pressure measurement, ECG, invasive arterial pressure measurement via cannulation of the radial artery, bispectral index (BIS) measurement, and end-tidal anesthetic gas concentrations. Systolic blood pressure (SBP), MBP, diastolic blood pressure (DBP), heart rate (HR), and BIS values were recorded every 5 min and final blood loss (mL/kg) was measured at the end of the surgery. Duration of surgery, duration of anesthesia, fluid infusion volume, mean remifentanil infusion rate (\( \mu g/kg/min \)) were also recorded. Autologous blood transfusion was started, if necessary, after the measurement of final blood loss. The values for SBP, MBP, DBP, HR, and BIS were calculated as mean values during surgery. The measurements are expressed as mean ± SD. An unpaired t-test was used for statistical analysis of SBP, MBP, DBP, HR,
coefficient of variation in mean blood pressure (CVMBP) during surgery, BIS, final blood loss, duration of surgery, duration of anesthesia, fluid infusion volume, and mean remifentanil infusion rate. A test of proportions was used to compare the coefficient of variation for blood loss. \( P < 0.05 \) was considered statistically significant.
Results

The mean age and male/female ratios were 25 years (17–50 years) and 10 males, 22 females in the Sevo group and 26 years (16–47 years) and 9 males, 23 females in the Iso group. Two patients in the Sevo group were classification ASA class II. No differences were observed between the two groups in terms of sex, age, height, weight, body mass index (BMI), duration of surgery, duration of anesthesia, and the total volume of local anesthetics (Table 1). Operations were performed by five surgeons, who have adequate experiences in orthognathic surgery. Distribution of the surgeons in the two groups was similar (Data not shown). The remifentanil infusion rate (µg/kg/min) was significantly lower in the Iso group compared with the Sevo group. The BIS value was also significantly lower in the Iso group compared with the Sevo group (Table 2).

Although no significant differences were observed between the groups for intraoperative HR, SBP, MBP, or DBP, CVMBP was significantly greater in the Iso group compared with the Sevo group (Table 2).

Intraoperative blood loss was 4.00±1.98 mL/kg in the Sevo group and 4.79±3.22 mL/kg in the Iso group. Although blood loss tended to be higher in the Iso
group, there was no significant difference between the two groups (Figure 1). No intraoperative adverse events were observed in this study.
Discussion

This study showed that although blood loss tended to be higher in the Iso group compared with the Sevo group, the difference was not significant. BIS value under anesthesia was lower in the Iso group compared with the Sevo group. Mean remifentanil infusion rate was less in the Iso group compared with the Sevo group. However, CVMBP was greater in the Iso group compared with the Sevo group.

Blood loss during surgery increases the risk of postoperative complications and blood transfusions. Various means of managing anesthesia have been considered in the past to reduce blood loss. Studies have shown that it is possible to reduce blood loss by maintaining intraoperative MBP at low levels,\(^{16}\) that blood loss is lower in patients with MBP maintained at 55–65 mmHg compared with those with MBP maintained at 75–85 mmHg,\(^{17}\) and that maintaining MBP at 65 mmHg provides appropriate conditions for surgical procedures and reduces blood loss.\(^{18}\) Circulation in vital organs can be maintained safely if MBP is 55 mmHg or above.\(^{19}\) We assumed that blood loss could be reduced and systemic circulation safely maintained if anesthesia were maintained with MBP at around 65 mmHg. Therefore, we maintained MBP at 60–65 mmHg in this study.
Balanced anesthesia, using combinations of inhalation anesthetics, intravenous anesthetics, and narcotic analgesics is now commonly practiced in general anesthesia. Remifentanil is often chosen as the narcotic analgesic during general anesthesia because it is an ultra-short acting and easily controllable opioid. The combined use of remifentanil with inhalation anesthetics allows sufficient pain relief and sedation at a low MAC because of drug interactions.\(^{20-22}\) In the clinical setting, one study reported that anesthesia can be maintained appropriately with continuous infusion of remifentanil at 0.1–0.3 µg/kg/min and the inhalation anesthetic maintained at 0.5–0.8 MAC.\(^{23}\) Rossi et al. investigated desflurane or sevoflurane maintained at 0.8 MAC under a concomitant use of 0.5 µg/kg/min remifentanil during orthognathic surgery and reported that blood loss was lower with desflurane anesthesia.\(^{14}\) We drew upon this research in our study to maintain anesthesia with the inhalation anesthetic at 0.8 MAC and remifentanil at 0.05–0.5 µg/kg/min.

Research has shown that volatile anesthetics exhibit different BIS values when maintained at the same MAC.\(^{24, 25}\) Olofsen et al. investigated the relationships of isoflurane and sevoflurane concentrations to BIS value and reported that the BIS value declined in a concentration-dependent manner up to a certain concentration of
anesthetic (isoflurane: 0.75% or approx. 0.65 MAC; sevoflurane: 1.5% or approx. 0.9 MAC), and then plateaued at around 40 for higher concentrations. The lower BIS value in the Iso group in our study may reflect the change in brainwaves caused by the inhalation anesthetic. However, although the BIS value was within the 40–60 range at the optimal depth of anesthesia, we cannot rule out the possibility that the level of anesthesia was deeper in the Iso group than in the Sevo group. However, because the objective of our study was to compare blood loss when the inhalation anesthetics were maintained at the same MAC and MBP was maintained at around 60 mmHg, we did not correct for differences in BIS value. If we assume that this difference in BIS value affects blood loss, we might expect blood loss to be higher in the Sevo group where Depth of anesthesia was light, but no difference was observed between the two groups in this study. Therefore, we believe that differences in BIS value did not have a major effect in this study.

The infusion rate to remifentanil in this study may have been less in the Iso group compared with the Sevo group because isoflurane dilates the blood vessels in a concentration-dependent manner and renders patients more likely to develop intraoperative hypotension. Hypotension may have occurred during the non-invasive
procedures in the Iso group, so the anesthesiologist may have reduced the infusion rate of remifentanil infusion rate. The dose might then have been insufficient for subsequent invasive surgical procedures, which may explain why CVMBP was larger in the Iso group compared with the Sevo group.

Research in rabbits has shown that isoflurane increased tissue blood flow in a concentration-dependent manner in the head and neck region, including bone marrow and alveolar tissues in the lower jaw, whereas sevoflurane produced no such change in mandibular bone marrow tissue. Özkiris et al. compared blood loss with the use of sevoflurane or isoflurane anesthesia in nasal septal surgery and reported higher blood loss with isoflurane. They explained that this occurs because isoflurane is a vasodilator that lowers arterial blood pressure in a concentration-dependent manner, and tissue blood flow increases because of vasodilation regardless of low perfusion pressure. Based on these studies, we had expected our comparison of anesthesia maintained with sevoflurane or isoflurane during surgery in the head and neck region to show greater blood loss with isoflurane because of its potent vasodilatory effect. However, no difference in blood loss was seen between the two groups in our study. The literature includes research on remifentanil-based anesthesia with desflurane or
sevoflurane during orthognathic surgery and remifentanil-based anesthesia with desflurane or isoflurane during ENT surgery. These studies reported no differences in blood loss with the different anesthetics and suggested that MBP affected blood loss. Remifentanil enables easy control of MBP while keeping hemodynamic variables stable. In this study as well, we were able to maintain intraoperative MBP at around our target of 65 mmHg by the combined use of remifentanil. Remifentanil also acts to reduce blood flow in an infusion rate-dependent manner at the site involved, such as in mandibular bone marrow tissue. Based on previous research in rabbits, we estimated blood flow in the mandibular bone marrow tissue and expected blood flow to be around 10% higher in the Iso group compared with the Sevo group. Although we could find a tendency towards higher blood loss in the Iso group, the difference between groups was not significant. This suggests that the decrease of blood flow in the mandibular bone marrow tissue induced by remifentanil was greater than the increase of that induced by isoflurane, such that any increase in tissue blood flow was suppressed and blood loss was not affected. However, CVMBP was higher in the Iso group than in the Sevo group in our study, which suggests that intraoperative MBP was unstable. This may have been
involved at least in part in the large variability of blood loss.

We did not directly measure intraoperative blood flow in the head and neck region in our study. Hence, we cannot determine whether changes in local tissue blood flow were involved in blood loss variability. The issues will need to be investigated from multifaceted perspectives because it is extremely difficult to measure tissue blood flow in the operative field in humans.

In this study, each group had 32 patients. This number may be small to detect the difference between two groups. Power analysis showed that about 200 patients were required in each group at the $\alpha$ error of 0.05 and $\beta$ error of 0.2. However, conversely, the difference in blood loss between two groups should be quite small and clinically negligible. Therefore, it is suggested that the reduction in tissue flow by remifentanil overcomes the increase in that by isoflurane.

In conclusion, in a comparison of intraoperative blood loss in remifentanil-based anesthesia with sevoflurane or isoflurane during orthognathic surgery, no difference was observed between the two groups.
Acknowledgement

The author would like to thank Prof. Ichinohe and Assistant Prof. Matsuura who provided constructive comments and suggestions for this study.
References


26. Olofsen E, Dahan A: The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology 90:1345, 1999


Figure legend

Fig. 1 Comparison of blood loss (mL/kg). Mean blood loss in the Sevo group was 4.00 ± 1.98 mL/kg, and that in the Iso group was 4.79 ± 3.22 mL/kg. There was no statistically significant difference between two groups. Data are shown as mean ± SD.
Table 1  Demographic Data

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<tr>
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<th>Iso Group</th>
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<tr>
<td>(n = 32)</td>
<td>(n = 32)</td>
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<tr>
<td>Age (yr)</td>
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<td>Height (cm)</td>
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<td>Weight (kg)</td>
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<td>BMI (kg/m²)</td>
<td>21.1 ± 2.3</td>
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<td>Duration of surgery (min)</td>
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<td>Duration of anesthesia (min)</td>
<td>386.3 ± 66.0</td>
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<td>Total volume of local anesthetics (mL)</td>
<td>24.4 ± 4.9</td>
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Data are presented as mean ± SD.
<table>
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<tr>
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<th>Iso Group</th>
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<td>(n = 32)</td>
<td>(n = 32)</td>
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<td>HR (beats/min)</td>
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<td>SBP (mmHg)</td>
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<td>MBP (mmHg)</td>
<td>64.0 ± 4.2</td>
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<td>CVMBP (%)</td>
<td>9.6 ± 2.2</td>
<td>11.2 ± 3.6*</td>
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<tr>
<td>DBP (mmHg)</td>
<td>49.3 ± 3.8</td>
<td>47.5 ± 3.6</td>
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<td>remifentanil infusion rate (µg/kg/min)</td>
<td>0.19 ± 0.06</td>
<td>0.14 ± 0.06*</td>
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<td>BIS value</td>
<td>50.5 ± 6.8</td>
<td>44.1 ± 6.4*</td>
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Data are presented as mean ± SD.

*Statistically significant difference between two groups (p<0.05).
Fig. 1

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<tr>
<th>Group</th>
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<tr>
<td>Sevo Group</td>
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<td>Iso Group</td>
<td>4.79 ± 3.22</td>
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