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The Effects of Oral Atenolol or Enalapril Premedication on Blood Loss and Hypotensive Anesthesia in Orthognathic Surgery

Na Young Kim,[1,2] Young-Chul Yoo,[1,2] Duk-Hee Chun,[3] Hye Mi Lee,[1] Young-Soo Jung,[4] and Sun-Joon Bai[1,2]

[1]Department of Anesthesiology and Pain Medicine, Severance Hospital,
[2]Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul;
[3]Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, CHA Bundang Medical Center, CHA University, Seongnam;
[4]Department of Oral and Maxillofacial Surgery, Oral Science Research Center, College of Dentistry, Yonsei University, Seoul, Korea.

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Corresponding author: Dr. Sun-Joon Bai, Department of Anesthesiology and Pain Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-4438, Fax: 82-2-2227-7897
E-mail: sjbai1@yuhs.ac

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Purpose: The aim of this study was to evaluate the effects of premedication with oral atenolol or enalapril, in combination with remifentanil under sevoflurane anesthesia, on intraoperative blood loss by achieving adequate deliberate hypotension (DH) during orthognathic surgery. Furthermore, we investigated the impact thereof on the amount of nitroglycerin (NTG) administered as an adjuvant agent. **Materials and Methods:** Seventy-three patients undergoing orthognathic surgery were randomly allocated into one of three groups: an angiotensin converting enzyme inhibitor group (Group A, n=24) with enalapril 10 mg, a β blocker group (Group B, n=24) with atenolol 25 mg, or a control group (Group C, n=25) with placebo. All patients were premedicated orally 1 h before the induction of anesthesia. NTG was the only adjuvant agent used to achieve DH when mean arterial blood pressure (MAP) was not controlled, despite the administration of the maximum remifentanil dose (0.3 μg $kg^{-1}min^{-1}$) with sevoflurane. **Results:** Seventy-two patients completed the study. Blood loss was significantly reduced in Group A, compared to Group C (adjusted p=0.045). Over the target range of MAP percentage during DH was significantly higher in Group C than in Groups A and B (adjusted p-values=0.007 and 0.006, respectively). The total amount of NTG administered was significantly less in Group A than Group C (adjusted p=0.015). **Conclusion:** Premedication with enalapril (10 mg) combined with remifentanil under sevoflurane anesthesia attenuated blood loss and achieved satisfactory DH during orthognathic surgery. Furthermore, the amount of NTG was reduced during the surgery.

Key Words: Atenolol, enalapril, premedication, blood loss, surgical, orthognathic surgery

INTRODUCTION

Various orofacial deformities have been corrected by orthognathic surgery. However, due to bony bleeding at the incision site and the intricacy of the orofacial blood

vessels, orthognathic surgery can involve significant intraoperative bleeding.[1,2] Further, intraoperative bleeding increases patient morbidity and mortality rates by extending surgical duration and time under anesthesia, as well as the amounts of blood transfusion required during surgery.[3]

Since the 1950s, deliberate hypotension (DH) has been used as an alternate method in maxillofacial surgeries to reduce blood loss and the need for a transfusion during surgery, as well as to improve the quality of the operative field through a reduction in mean arterial blood pressure (MAP).[4,5] In order to achieve DH, various agents, including sodium nitroprusside (SNP), nitroglycerin (NTG), and inhalation anesthetics have been successfully employed.[6,7]

Nevertheless, reflex tachycardia, caused by the direct peripheral vasodilation effects of SNP, increases myocardial oxygen demand and makes the control of blood pressure difficult.[6,8,9] Also, NTG is not as effective as SNP in reducing bleeding after achieving adequate DH, despite the fact that NTG has a better benefit/risk ratio than SNP.[6] While the use of inhalational anesthetic drugs facilitates the successful achievement of DH, high concentrations of anesthetic agents are required to achieve adequate DH, which can lead to liver or kidney toxicity.[6]

In this randomized, double-blind, placebo-controlled study, we hypothesized that preoperative administration of oral atenolol or enalapril, in combination with remifentanil under sevoflurane anesthesia, would reduce intraoperative blood loss by achieving adequate DH in orthognathic surgery. Furthermore, we evaluated the effects thereof on the amount of NTG administered as an adjuvant agent.

MATERIALS AND METHODS

Study design

This study was approved by the Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital, Yonsei University Health System, Seoul, Korea (4-2012-0422) and was registered with the Clinical Research Information Service (registration number NCT 01839253). Informed consent was obtained from 73 patients (American Society of Anesthesiologists I–II physical status, aged 18–29 years) who were to undergo orthognathic surgery between April 2013 and March 2014. Patients with hypertensive disease, previous treatment with diuretics or hypertensive drugs, coronary artery diseases, chronic renal failure, hepatic failure, drug hypersensitivity, neurological or psychiatric illness, symptomatic asthma, or who were taking medication for the treatment of a systemic disease were excluded.

Randomization and allocation

The patients were randomly assigned to one of three groups using a computer-generated table of random numbers: the angiotensin converting enzyme (ACE) inhibitor group (Group A, n=24) received 10mg of enalapril; the β-blocker group (Group B, n=24) received 25 mg of atenolol; and the control group (Group C, n=25) received a placebo tablet (vitamin complex) 1 h before the induction of anesthesia. An anesthesiologist who was not involved in the study administered the drug tablet directly into the mouths of the patients and monitored for enalapril side effects, including dry cough, diarrhea, headache, and nausea, or for the side effects of atenolol, such as chest pain, arrhythmia, bradycardia, orthostatic hypotension, confusion, tingling, numbness in the extremities, diarrhea, abdominal discomfort, nausea, and allergic reactions.[10,11] The investigator, surgeons, attending anesthetist, patients, and recovery nurses were blinded to group allocation.

Procedure

Patients received 0.1 mg of glycopyrrolate intravenously for premedication. After arrival in the operating room, anesthesia was induced with 2 mg kg^{-1} of propofol, 0.6 mg kg^{-1} of rocuronium, and 0.05–0.1 μg kg^{-1} of remifentanil following non-invasive blood pressure monitoring, electrocardiography, and measurement of oxygen saturation (SpO_2). After nasotracheal intubation, the patients' lungs were mechanically ventilated with a tidal volume of 8 mL kg^{-1} of ideal body weight at 50% air with oxygen, and the respiratory rate was adjusted to maintain the end-tidal carbon dioxide tension at 35–40 mm Hg. Radial artery catheterization was performed for continuous blood pressure monitoring and arterial blood gas analysis. The MAP and heart rate (HR) were monitored continuously. In addition, the cardiac index (CI) was measured by applying a FloTrac/Vigilio™ system (Edwards Lifesciences, Irvine, CA, USA) via connection of the arterial cannulation for cardiac output monitoring.

DH was induced at the mucosal incision until the surgeon's request after completion of the main surgical procedures; to achieve a MAP within the target range of 55–65 mm Hg, inhalation anesthesia was maintained with sevoflurane at an age-adjusted minimal alveolar concentration of 1.0, and remifentanil was infused until its dose increased to 0.3 μg $kg^{-1}min^{-1}$.[12,13] NTG was the only adjuvant agent used to achieve DH when MAP was not controlled, despite the admin-

istration of the maximum remifentanil dose (0.3 μg kg^{-1} min^{-1}) with sevoflurane. Additionally, we calculated the target range of MAP percentage during DH. An over target range of MAP percentage was considered as the period in which the MAP was >65 mm Hg, while an under target range of MAP percentage was the period in which the MAP was <55 mm Hg. All ranges of MAP percentage were calculated using the 1-min interval of MAP by Philips monitoring device. Further, hematocrit (Hct) was maintained at >27% throughout the surgery.

Intraoperative fluid amounts, urine output, and blood loss were recorded hourly. Blood loss was estimated by measuring suction bottle drainage, surgical drapes, and by weighing gauze sponges. Intraoperative fluid was maintained using Lactated Ringer's Solution at a constant rate of 5–10 mL kg^{-1} h^{-1}. When blood loss exceeded 300 mL, 6% hydroxyethyl starch solutions (Voluven, Fresinius Kabi, Bad Homberg, Germany) was administered at a 1:1 ratio, and if Hct was <27%, a transfusion was initiated. Hypotension (MAP<55 mm Hg) was treated with 10 μg of intravenous phenylephrine. At the time of mucosal suturing, 1 μg kg^{-1} of fentanyl and 0.3 mg of ramosetron were administered to all patients for postoperative pain and as an antiemetic, respectively. A blinded investigator monitored patient hemodynamics and any adverse effects during postoperative 24 hours.

Statistical analysis

Sample sizes were calculated based on a previous study,[13] in which the mean±SD difference of intraoperative blood loss in the hypotensive group was 454.0±211.3 mL, and the corresponding value for the control group was 755.3±334.6 mL. In order to detect 301.3 mL of blood loss between the three groups (α=0.05, power=80%), 22 patients were required for each group. Considering a 10% dropout rate, 25 patients were recruited for each group.

All statistical analyses were performed using IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables and categorical variables were presented as the mean±SD and numbers, respectively. Parametric data were analyzed with one-way analysis of variance with Bonferroni correction for multiple comparisons. The MAP, HR, and CI values were analyzed using a linear mixed model at 11 separate time points (Table 1). Differences over time among the three groups were analyzed using a group by time interaction. When statistical significances were detected in the repeated measures, post-hoc analyses using Bonferroni correction for multiple comparisons were performed. The analysis of non-normally distributed phenylephrine data was performed using the Kruskal-Wallis test. Chi-square test or Fisher's exact test was used to analyze categorical variables. All *p*-values<0.05 were regarded as statistically significant.

Table 1. Time Points for Hemodynamic Parameter Measurements

Time point	Event
T0	Baseline before premedication
T1	Before induction of anesthesia after premedication
T2	Just after induction of anesthesia
T3	30 min after the induction of DH
T4	60 min after the induction of DH
T5	90 min after the induction of DH
T6	120 min after the induction of DH
T7	5 min after the end of DH
T8	Immediately after extubation in the operating room
T9	60 min after extubation in the PACU
T10	60 min after discharge from the PACU in the admission room

DH, deliberate hypotension; PACU, post anesthetic care unit.

Fig. 1. CONSORT flow diagram. Group A, angiotensin converting enzyme inhibitor group; Group B, β-blocker group; Group C, control group.

RESULTS

A total 75 patients were accessed for eligibility, and two patients with previous cardiac surgery and hypertension were excluded. Seventy-three patients were randomized into three groups. One patient in Group A was excluded due to a change in the surgical plan. The remaining 72 patients completed the study without any complications (Fig. 1). Patients un-

derwent simultaneous bimaxillary orthognathic surgery, including Lefort I osteotomy and mandibular ramus osteotomy. Additionally, 17 patients in Group A, 15 patients in Group B, and 14 patients in Group C underwent additional genioplasty. The differences in the number of patients in the groups that underwent additional genioplasty were not statistically significant.

Demographic data are shown in Table 2. The weights and body mass indices were significantly different among the three groups. Further, the results indicated that the values for both measurements were higher in Group C than in Group B (adjusted p=0.010). There was no significant difference in preoperative and postoperative Hb levels between the three groups.

Intraoperative data are presented in Table 3. The total duration of surgery was similar among the groups; however, there was a significant difference in the duration of DH among the three groups. The duration of DH in Group C was longer than that of Group B following post-hoc analysis with Bonferroni correction (adjusted p=0.026). Furthermore, the over target range percentage during DH was significantly higher in Group C than in Groups A and B (adjusted p-values=0.007 and 0.006, respectively). In addition, the amount of NTG used during DH was less in Group A than Group C (adjusted p=0.015). There was no difference in the amount of remifentanil administered during DH among the three groups. Similarly, despite the fact that Group A required more phenylephrine than the other groups, the difference was not statistically significant.

Hemodynamic changes at each time point are shown in Figs. 2 and 3. Significant differences over time in MAP were observed among the three groups, following analysis using a linear mixed model (p=0.0016) (Fig. 2). The results of Bonferroni post-hoc comparisons for repeated measures indicated a pattern of significant differences in MAP at T1 between Group A and C (adjusted p=0.0561). In addition, MAP at T1 was statistically lower in Group B than Group C (adjusted p<0.001), and MAP at T7 was significantly higher in Group C than Group A (adjusted p<0.001). HR and CI values are shown in Fig. 3. There were significant overall differences in the HR values among the three groups, regardless of time, following analysis using a linear mixed model. The results of post-hoc analysis using Bonferroni correction indicated that HR of Group B was significantly lower than that

Table 2. Patient Characteristics According to Preoperative Agent

	Group A (n=23)	Group B (n=24)	Group C (n=25)	p value
Gender (M/F)	11/12	8/16	15/10	0.194
Age (yrs)	22.6±3.5	21.6±3.1	21.7±2.9	0.475
Weight (kg)	60.5±10.9	57.4±9.7	66.8±11.9	0.011*
Height (cm)	168.2±9.7	166.2±7.8	169.3±7.1	0.401
BMI (kg/m^2)	21.3±2.3	20.8±2.8	23.2±3.3	0.008*
ASA physical status I/II	21/2	24/0	23/2	0.457
Preoperative Hct (%)	34.96±3.5	34.08±3.1	36.28±3.4	0.082

BMI, body mass index; ASA, American Society of Anesthesiologists; Hct, hematocrit; A, angiotensin converting enzyme inhibitor; B, β-blocker; C, control.
Data are presented as means±standard deviation or as numbers.
*p<0.05.

Table 3. Intraoperative Data on DH According to Preoperative Agent

	Group A (n=23)	Group B (n=24)	Group C (n=25)	p value
Duration of surgery (min)	276.7±63	264.1±64.8	271.0±52	0.769
Duration of DH (min)	179.1±57.4	155.8±40.1	192.0±44.1	0.032*
Over target range percentage during DH (%)	13.9±11.3	13.8±7.0	23.2±11.7	0.002*
Target range percentage during DH (%)	74.4±10.5	76.0±12.5	68.7±12.1	0.079
Under target range percentage during DH (%)	11.6±9.4	10.3±7.3	8.1±7.5	0.321
Remifentanil amounts during DH (μg/kg/min)	0.07±0.12	0.06±0.10	0.06±0.12	0.927
NTG amounts during DH (μg/kg/min)	3.2±12.7	6.2±16.9	18.4±23.7	0.012*
Patients administered phenylephrine during DH (n)	6	5	4	0.668
Phenylephrine amounts during DH (μg)	0 (0–300)	0 (0–70)	(0–50)	0.634

DH, deliberate hypotension; NTG, nitroglycerin; A, angiotensin converting enzyme inhibitor; B, β-blocker; C, control.
Data are presented as means±standard deviation, numbers or median range.
*p<0.05.

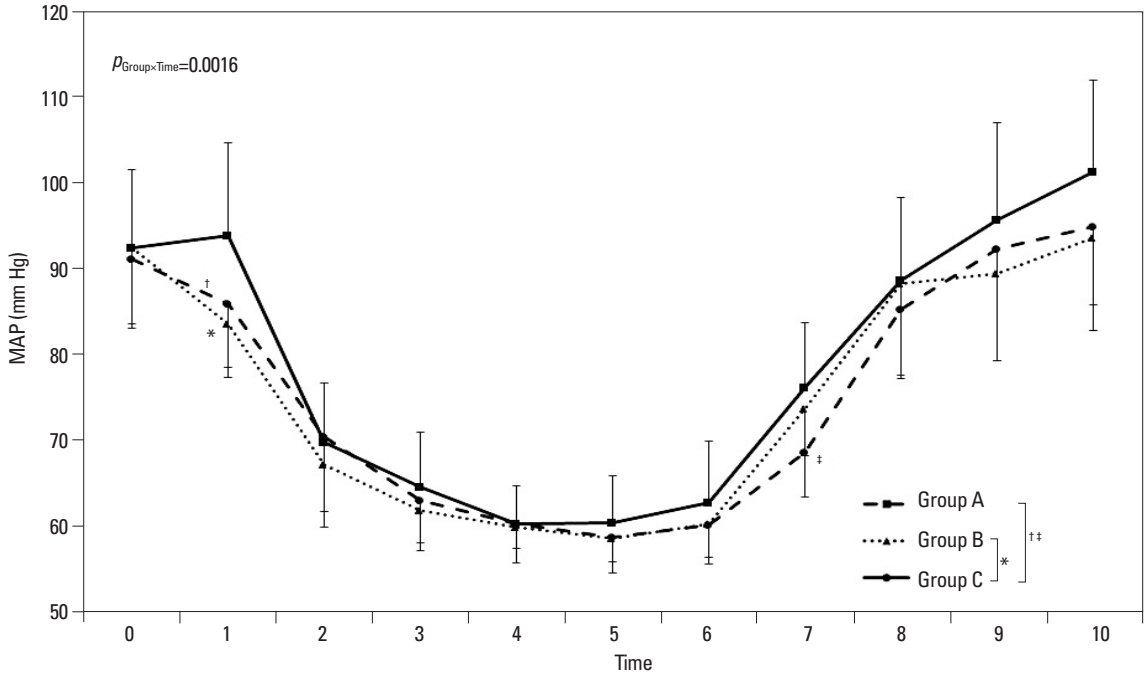

Fig. 2. Mean arterial blood pressures (MAP) in Group A, B, and C at each time point, as described in Table 1. Significant differences over time in MAP were observed among the three groups following analysis using a linear mixed model. The results of Bonferroni post-hoc comparisons for repeated measures indicated a pattern of significant difference in MAP at T1 between Group A and C (adjusted p=0.0561). In addition, MAP at T1 was statistically lower in Group B than Group C (adjusted p<0.001) and MAP at T7 was significantly higher in Group C than Group A (adjusted p<0.001). Group A, angiotensin converting enzyme inhibitor group; Group B, β-blocker group; Group C, control group. *,‡Adjusted p<0.05, †Adjusted p<0.1.

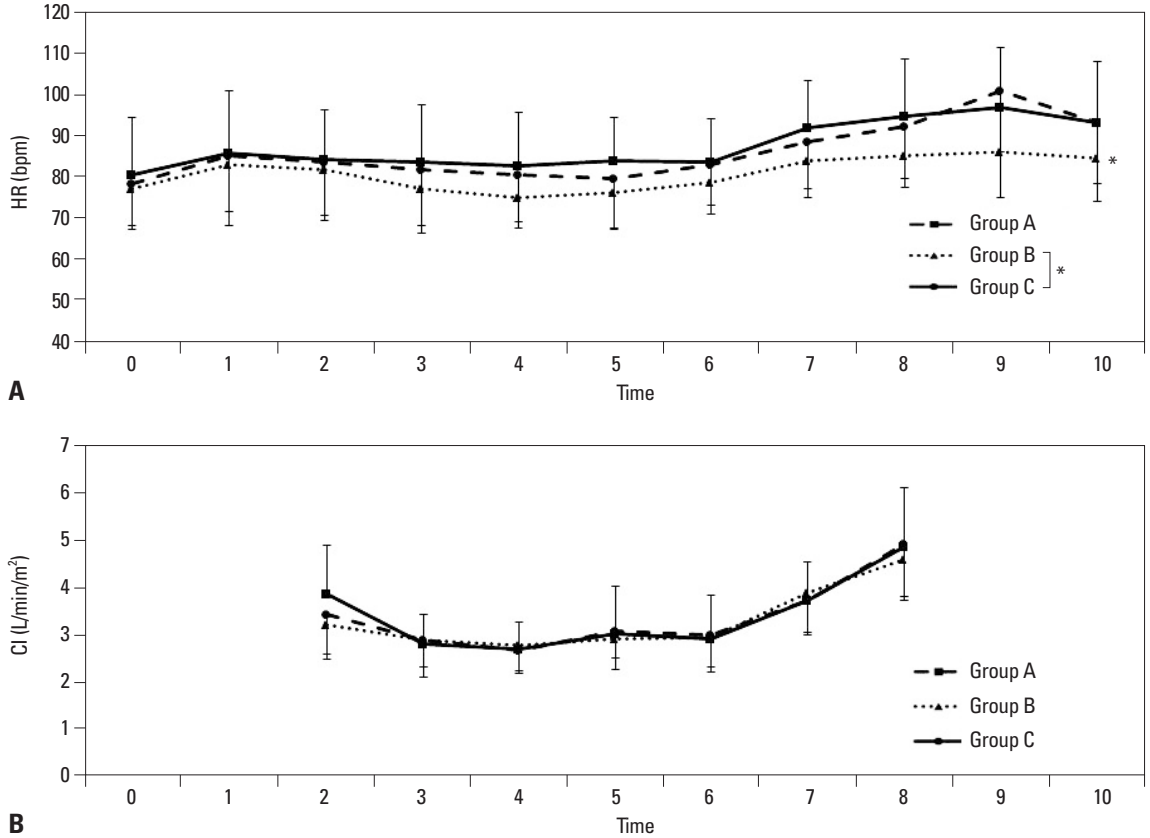

Fig. 3. (A) Heart rate (HR) and (B) cardiac index (CI) in Groups A, B, and C at each time point, as shown in Table 1. Analysis using a linear mixed model indicated significant overall differences among the three groups, regardless of time. After post-hoc analysis with Bonferroni correction, the HR of Group B was significantly lower than that of Group C (adjusted p=0.0213). Furthermore, there was no significant difference in CI among the three groups at any of the time points analyzed. Group A, angiotensin converting enzyme inhibitor group; Group B, β-blocker group; Group C, control group. *Adjusted p<0.05.

Table 4. Intraoperative Blood Loss, Fluid Amounts, and Urine Output According to Preoperative Agent

	Group A (n=23)	Group B (n=24)	Group C (n=25)	*p* value
Intraoperative bleeding (mL)	720±254.4	793±418.1	1030±555.1	0.038*
Intraoperative autologous blood transfusion (pack)	0.35±0.57	0.38±0.65	0.60±0.91	0.421
Crystalloid (mL)	1743.5±469.8	1737.5±504.8	1744±565.6	0.999
Colloid (mL)	647.8±354.0	702.1±469.9	734.0±387.5	0.762
Total fluid (mL)	2391.3±685.1	2439.6±666.8	2478.0±825.6	0.911
Total urine output (mL)	588.0±389.8	389.8±165	540.4±347.1	0.085
The length of postoperative hospital stay (days)	3.26±0.54	3.33±0.57	3.36±0.70	0.845

A, angiotensin converting enzyme inhibitor; B, β-blocker; C, control.
Data are presented as means±standard deviation.
*$p<0.05$.

of Group C (adjusted $p=0.0213$). Furthermore, no significant differences were detected in CI among the three groups at any time point.

Total intraoperative blood loss was significantly less in Group A than in Group C (adjusted $p=0.045$) (Table 4). However, there was no significant difference in the amount of intraoperative autologous blood transfusion among the three groups. Total volume of fluid administered and urine output were comparable among the groups. No patients suffered from hemodynamic instability or any other complications.

DISCUSSION

The results of the current study indicated that preoperative medication with 10 mg of enalapril attenuated blood loss and achieved satisfactory DH during orthognathic surgery under balanced anesthesia with remifentanil and sevoflurane, while premedication with 25 mg of atenolol did not significantly reduce intraoperative blood loss. Further, enalapril was effective in reducing the amount of NTG adjuvant agent administered during the surgery.

Currently, DH is used for surgeries that require the transfusion of a large amount of blood[14] and for attaining a bloodless surgical field.[6] Additionally, a number of previous reports have indicated that DH is likely to cause a significant reduction in intraoperative blood loss.[2,15,16] In order to induce DH under general anesthesia, various different combinations of agents and primary inhalation anesthetics have been used.[17]

Inhalation agents produce vasodilatory effects in a dose dependent manner, and can affect intraoperative blood loss due to associated pharmacologic effects.[11] Also, when used alone, high concentrations of inhalation anesthetics are needed to achieve adequate hypotension, which can lead to liver or kidney toxicity.[6] Vasodilators, such as SNP and NTG, are the most commonly used hypotensive agents.[6] However, intraoperative administration of SNP can trigger direct vasodilation effects that in turn cause a reduction in venous return. Peripheral vasodilatation results in baroreceptor-induced reflex tachycardia and an increase in myocardial contractility. The sympathetic and renin-angiotensin systems are also activated, and are responsible for the rebound hypertension that causes perioperative hemodynamic derangement.[6] The endocrine responses related to NTG-induced hypotension are contradictory in terms of plasma catecholamine levels, most likely due to differences in the magnitude of the surgical stress, blood loss, and the level and duration of hypotension.[18] If adequate hypotension levels are not obtained during surgery, intraoperative blood loss can be more severe. A number of previous studies have proposed premedication with a β-blocker in combination with SNP during DH for the reduction of reflex tachycardia and rebound hypertension.[8,19,20] However, to the best of our knowledge, no prior studies have investigated the impact of a preoperative oral β-blocker or ACE inhibitor administration on the intraoperative blood loss or achievement of adequate DH when combined with intraoperative NTG as an adjuvant agent under balanced anesthesia.

The primary objective of this study was to evaluate whether preoperative treatment with a β-blocker or ACE inhibitor could significantly reduce total blood loss during surgery. The intraoperative blood loss was significantly lower in Group A (720±254.4 mL) than Group C (1030±555.1 mL). Although Group B exhibited an average blood loss of 793±418.1 mL, which was lower than that in in Group C, the difference was not statistically significant. Therefore, premedication with oral enalapril under general anesthesia could attenuate blood loss during orthognathic surgery.

In the present study, the duration of DH was significantly longer in Group C than Group B, despite the fact that there were no significant differences in the duration of surgery.

This may be because blood pressure in Group C increased immediately after the end of DH. At this time, 4 patients in Group C developed persistent oozing and bleeding due to the acute elevation of MAP; DH was restarted upon the surgeon's request and the remainder of the procedure was performed while DH was maintained. This indirectly implies that the surgical time during DH was prolonged due to the poor quality of the operative field. In addition, over target range percentage was significantly higher in Group C than in the other groups. Despite the lack of statistical significances, the target range percentage was the lowest in Group C, and the under target range percentage was the highest in Group A. In regards to hemodynamic changes, the target range for DH was 55–65 mm Hg, because DH should not adversely affect the blood supply to vital organs and end-organ perfusion and tissue oxygenation must be maintained.[12,13] No severe hemodynamic instability was noted in either group. The MAPs after premedication exhibited a significantly lower pattern in the premedication groups compared to the control group: MAP at T1 time point (before induction of anesthesia after premedication) exhibited a significantly lower pattern between Groups A and C. Further, even after post-hoc analysis, MAP at T1 was significantly lower in Group B than in Group C. However, there were no statistical differences among the three groups in the frequency of hypotension after induction of anesthesia (T2). In addition, MAP after termination of DH tended to be higher in Group C than the premedication groups: MAP at T7 (5 min after the end of DH) was significantly higher in Group C than Group A, even after post-hoc analysis. Enalapril may be a more suitable premedication agent to stabilize MAP after the end of DH and postoperative blood pressure, because of its pharmacodynamic profile.[21] Acute elevation of MAP at the end of DH may increase the risk of re-bleeding, thus stabilization on the MAP of post-DH would be clinically beneficial. Also, there were no statistically significant differences among three groups in the HR and CI before and after premedication, as well as at the induction of anesthesia.

Administration of NTG causes nonspecific, direct vasodilation of venous capacitance vessels, and incidental vasodilation in arteries.[22] NTG also increases venous blood volume and decreases venous return, which consequently results in a proportional reduction in cardiac output. Since total blood volume can affect decreases in blood pressure, an excessive drop in blood pressure could occur in patients with a low blood volume, and coronary blood flow could be compromised. In addition, responses to NTG, when compared with SNP, are slower; thus, NTG is not as effective for achieving adequate DH.[6] Accordingly, other adjuvant agents may be required especially in young patients.[23] In the present study, NTG was only infused when the target range blood pressure was not achieved using anesthetic agents alone. Group A required the use of significantly lower amounts of NTG than Group C. This result may have clinical significance, as premedication with enalapril not only caused significant attenuation of intraoperative blood loss, but also resulted in decreased reliance on NTG to achieve adequate DH, which could lead to a reduction in adverse NTG effects. However, there were no significant differences in the mean amounts of remifentanil administered during DH among the three groups ($\mu g\ kg^{-1}min^{-1}$). Remifentanil was used to control the target range MAP by incremental adjustment of the dose to 0.3 $\mu g\ kg^{-1}min^{-1}$. NTG was added only when MAP was not controlled despite administration of the maximum remifentanil dose to stabilize MAP during DH. However, administration of the maximum remifentanil dose (0.3 $\mu g\ kg^{-1}min^{-1}$) was not required throughout the DH period, which explains why there were no statistically significant differences among the three groups in the mean amounts of remifentanil administered during DH (0.06–0.07 $\mu g\ kg^{-1}\ min^{-1}$). In addition, there was no statistical difference in the number of patients who were administered phenylephrine and phenylephrine amounts during DH among the three groups, even though Group A required more phenylephrine.

The current study has some limitations. Despite no differences in the lengths of the postoperative hospital stay among the three groups, postoperative edema and recovery time should have been evaluated, and evaluation on the quality of the surgical field during DH should have been rated by the surgeon. In addition, there were no statistical differences among the three groups in the amount of intraoperative autologous blood transfusions, even though blood loss was significantly greater in Group C than in the other groups. Likely explanations include the possibility that some patients became anemic following pre-operative autologous donation, and that Hct dropped below 27% in those patients without severe bleeding. Accordingly, the fact that preoperative Hct in Group C was higher than in Groups A and B, despite a lack of statistically significant differences, might have affected the amounts of intraoperative blood transfusion required. Lastly, it is difficult to confirm that the doses of both drugs were equivalent, even though the doses were the same as those used in previous studies that compared the efficacy of enalapril and atenolol.[24,25] Consequently, poten-

tial differences in the drug doses might explain why the reduction in blood loss achieved with atenolol was not statistically significant. Further efforts should be made to assess factors, such as patient recovery time and surgical field rating, as well as to identify other potential influencing factors.

In conclusion, while premedication with 25 mg of atenolol did not significantly reduce intraoperative blood loss, preoperative administration of 10 mg of enalapril attenuated blood loss and achieved satisfactory DH during orthognathic surgery under balanced anesthesia with remifentanil and sevoflurane. Furthermore, preoperative treatment with enalapril led to a reduction in the amount of NTG adjuvant agent required during surgery.

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