Effects of remifentanil with or without midazolam pretreatment on the 95% effective dose of propofol for loss of consciousness during induction
A randomized, clinical trial
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Abstract
Background: Propofol is a rapid, efficient hypnotic agent with antiemetic effects. However, a high dosage is related to hemodynamic abnormalities such as hypotension and bradycardia. Pretreatment with remifentanil can decrease injection pain and stabilize hemodynamics during the induction period. Remifentanil or midazolam in combination with propofol can provide synergistic or additive effects during anesthesia induction. However, the hypnotic doses of propofol required in patients who receive pretreatment with remifentanil or midazolam remain unclear.

Methods: Patients aged 20 to 50 years who were scheduled to undergo surgery under general anesthesia were enrolled in this study. The patients were randomized into 3 groups using a computer-generated randomization table. Patients in Group P (Propofol) received only propofol for loss of consciousness, those in Group PR (Propofol-Remifentanil) received remifentanil prior to propofol, and those in Group PMR (Propofol-Midazolam-Remifentanil) received remifentanil and midazolam prior to propofol. After propofol administration, loss of both the eyelash reflex and verbal response represented success. The 95% effective dose of propofol for loss of consciousness in each group, which was the primary outcome, was determined using a modified biased coin up-and-down method.

Results: A total of 124 patients were initially enrolled. Of these, 4 were excluded, and the remaining 120 patients were randomized to each (n=40) of the 3 groups. The 95% effective dose of propofol for loss of consciousness was 1.74, 1.38, and 0.92 mg/kg in Groups P, PR, and PMR, respectively. Blood pressure decreased at 2 minutes after propofol administration in all the groups. However, compared with Group P, Groups PR and PMR exhibited a significant decrease in blood pressure.

Conclusions: The effective dose of propofol for loss of consciousness could be decreased by 21% and 47% when remifentanil pretreatment was used without and with midazolam, respectively. However, the decrease in blood pressure was greater with pretreatment than sole propofol use. These findings suggest that the combination of remifentanil with or without midazolam may have no benefit on hemodynamic stability during induction using propofol.

Trial registration: NCT02536690 (clinicaltrials.gov).

Abbreviations: ANOVA = analysis of variance, ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval, ED95 = 95% effective dose, HR = heart rate, MBP = mean blood pressure, SpO2 = oxygen saturation.

Keywords: effective dose, intravenous anesthesia, loss of concentration, midazolam, propofol, remifentanil, up and down
1. Introduction

Propofol is a rapidly acting, unpungent hypnotic agent with antiemetic properties. Several anesthesiologists use this agent for the induction of general anesthesia. However, a high dosage is related to hypotension and/or bradycardia, with possible underlying mechanisms including the negative inotropic or peripheral vasodilation effects of propofol. Therefore, the use of propofol for the induction of anesthesia in patients with susceptible comorbidities can lead to the occurrence of serious and dangerous cardiovascular complications.

Previous studies reported that opioids or benzodiazepines used in combination with propofol provided additive or synergistic effects that could decrease the required dose of propofol for several procedures. Midazolam is a benzodiazepine commonly used as a pretreatment agent to decrease anxiety and improve patient satisfaction levels. Remifentanil is an opioid used for intraoperative pain control. Pretreatment with remifentanil can decrease injection pain and provide hemodynamic stability during the induction period. However, the required bolus dose of propofol for loss of consciousness during induction in patients who receive pretreatment with remifentanil or midazolam remains unclear. Furthermore, the effects of premedication with remifentanil or midazolam on the patient’s hemodynamics have not been elucidated.

Therefore, in this randomized controlled trial, we investigated and compared the effects of no pretreatment, remifentanil pretreatment, and remifentanil plus midazolam pretreatment on the 95% effective dose (ED95) of propofol for loss of consciousness during induction.

2. Methods

This study was approved by the Institutional Review Board (approval no: 2015-0183-004) of Gangnam Severance Hospital, Seoul, Korea and registered at clinicaltrials.gov (NCT02536690). A total of 124 patients (age, 20–50 years) scheduled for surgery under general anesthesia were enrolled in this study. Patients with an American Society of Anesthesiologists (ASA) physical status of III or IV, those with a history of adverse effects caused by the study drugs, and those with a body mass index of ≥30kg/m² were excluded.

After obtaining informed consent from all the patients, we randomized them into 3 groups using a computer-generated randomization table. Before transfer to the operation room, an 18-gauge intravenous catheter was inserted at the patient’s basilic vein and 5mL/kg of 0.9% normal saline was infused before the induction. Intravenous glycopyrrolate 0.2mg was administered as premedication to all the patients. In the operating room, the patients were monitored with electrocardiography, pulse oximetry, noninvasive blood pressure measurements, and multigas analysis.

Each patient received intravenous propofol after 3 minutes of preoxygenation. In Group P (Propofol), no additional drug except propofol was used for the induction. In Groups PR (Propofol-Remifentanil) and PMR (Propofol-Midazolam-Remifentanil), remifentanil 0.25µg/kg/min was intravenously infused from the start of preoxygenation until 2 minutes after propofol administration. In Group PMR, intravenous midazolam 0.05µg/kg was additionally administered 1 minute after preoxygenation.

After the predetermined dose of propofol was administered, loss of the eyelash reflex and verbal response was assessed for 2 minutes. Induction success was represented by loss of both the eyelash reflex and verbal response. Other cases were considered failures.

The dose of propofol used for each patient was determined according to the success or failure of induction in the previous patient using a modified biased coin up-and-down method. The initial dose was set as 1.0mg/kg for each group; this was the least successful hypnotic dose of propofol in a previous study. If induction failed in 1 patient, the dose for the next patient was increased by 0.25mg/kg. If induction was successful in 1 patient, the dose for the next patient was determined by a randomly selected card from a total of 19 cards. With a probability of 1/19, the dose for the next patient was decreased by 0.25mg/kg, and the same dose was administered with a probability of 18/19.

The mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO2) of all the patients were recorded at baseline, before propofol administration, and 1 and 2 minutes after propofol administration. Any adverse effects were monitored and recorded.

2.1. Statistical analysis

A minimum of 40 subjects were required according to simulation based on the methods by Durham et al. Therefore, we included 40 patients in each group in the present study.

All the statistical analyses were performed using the R for Windows (version 3.2.0; The R Foundation for Statistical Computing; https://www.r-project.org) for isotonic regression and SAS (version 9.2; SAS Institute, Cary, NC) for linear mixed-model analyses and analysis of variance (ANOVA). To derive regression models allowing the prediction of the effective dose of propofol for the successful loss of consciousness in 95% patients (ED95), isotonic regression using the pooled adjacent violators algorithm (PAVA) was performed for each group. A bootstrapping approach to produce 95% confidence intervals (CIs) was used for the estimates of ED95. ANOVA and a linear mixed model were used to analyze the demographic characteristics and hemodynamic changes for each group. A P value of <.05 was considered statistically significant.

3. Results

From the total of 124 patients, 4 refused to participate in the study. The remaining 120 patients were equally randomized (n = 40 each) into the 3 groups.

The demographic characteristics of the enrolled patients are shown in Table 1. There were no significant differences in any characteristic among the 3 groups. The allocation sequence for each group according to the biased coin design is demonstrated in Fig. 1. The PAVA response rate for each group is shown in Fig. 2. For the higher success rate for loss of consciousness, Group P required higher dose of propofol, followed by Group PR and Group PMR. The ED95 of propofol was 1.74, 1.38, and 0.92mg/kg in Groups P, PR, and PMR, respectively (Table 2). MBP and HR measured at each time point are shown in Fig. 3. In all the groups, MBP was decreased at both 1 and 2 minutes after propofol administration compared with baseline (P < .001 for all the groups at each time). However, in Group PMR, MBP was also decreased before propofol administration (P < .001). Though there were no intergroup differences at other time points, MBP was more significantly decreased at Groups PR and PMR compared with Group P at 2 minutes after propofol administration (P < .02 and P < .01, respectively).
Compared with the baseline value, HR exhibited a significant decrease at 0, 1, and 2 minutes after propofol administration only in Group PMR ($P < .001$). In Group PR, the HR decreased at 2 minutes after propofol administration compared with baseline. However, HR exhibited a significant decrease at 1 minute ($P = .05$ compared with that before propofol administration), followed by a further significant decrease at 2 minutes ($P < .001$ compared with that at 1 minute) in Group PR. There were no intergroup differences in HR at each time point. No adverse effects related to the administered drugs were recorded.

### Table 2

| Group    | $E_{95}$ (mg/kg) | 95% CI  |
|----------|------------------|---------|
| P        | 1.74             | 1.61–2.34 |
| PR       | 1.38             | 1.23–1.61 |
| PMR      | 0.92             | 0.79–1.13 |

Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.25μg/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05μg/kg) and remifentanil prior to propofol.

$CI =$ confidence interval, $E_{95} =$ 95% effective dose. 

**4. Discussion**

In this randomized controlled trial, we investigated and compared the effects of no pretreatment (Group P), remifentanil pretreatment (Group PR), and remifentanil plus midazolam pretreatment (Group PMR) on the $E_{95}$ of propofol on patients aged 20 to 50 years old for loss of consciousness during induction. The results indicated that the required hypnotic dose of propofol was lower when the patients received pretreatment with remifentanil or both remifentanil or midazolam. However, MBP and HR decreased more with pretreatment than without pretreatment.

Some studies have reported the propofol dose-sparing effects of remifentanil and midazolam. The findings of our study were consistent with the findings of these previous studies.\[3,4,6\]

Pretreatment with remifentanil during induction has some advantages. The optimal dosage of remifentanil pretreatment can offer hemodynamic stability during maneuvers in the induction period, including laryngoscopy and intubation,[9,10] and it was also shown to have protective effects on organs in animal studies.\[13–15\] In addition, it is reported that remifentanil
pretreatment can prevent pain caused by propofol injection. A few studies used target-controlled infusion to investigate the hypnotic dose of propofol when combined with remifentanil and the effects of combined treatment on hemodynamics.\[^{3,6}\] Target-controlled infusion requires special equipment that needs time to be set up. In addition, this technique may not be accurate in situations where several drugs are used in combination, particularly in the induction period.\[^{11}\] In clinical practice, several clinicians administer the study drugs according to the patient’s weight. Therefore, we designed this study using weight-based calculations for the drug dose.

Previous studies have suggested that propofol should be administered at lower doses in the elderly or when used in combination with other agents.\[^{4-6,17}\] Nevertheless, several clinicians still use an induction dose of up to 2.5 mg/kg (ED$_{95}$ of propofol), even when midazolam or remifentanil are administered for premedication and analgesia during the induction period.\[^{17}\] A possible reason could be the lack of clinical data on the ED$_{95}$ of propofol when used in combination with midazolam or remifentanil. The findings of our study suggest that the ED$_{95}$ of propofol can be decreased in patients who receive pretreatment.

Although we were able to lower the propofol dose for loss of consciousness by remifentanil pretreatment with or without midazolam, the decrease in MBP and HR was greater with pretreatment than without pretreatment. Remifentanil is often used to induce hypotension during surgery.\[^{18,19}\] The decrease in blood pressure is thought to be due to a decrease in the regional vascular tone.\[^{20}\] However, remifentanil is known for better maintenance of hemodynamic stability and the cerebral blood flow compared with other currently used opioids.\[^{21}\] Although the decrease in blood pressure becomes more conspicuous when it is administered in combination with propofol,\[^{12}\] in the present study, blood pressure did not decrease until propofol was administered in Groups P and PR, whereas it began to decrease before propofol was administered in Group PMR. Midazolam does not usually decrease blood pressure when used alone.\[^{23}\] The decrease in MBP observed before propofol administration in Group PMR in the present study can be attributed to a decrease in anxiety induced by midazolam.\[^{7}\] However, because the initial MBP of the study subjects was in the normal range of 88.2 mm Hg, there is a possibility that midazolam synergized with remifentanil to cause the decrease in blood pressure.\[^{24}\] Further studies would provide a more clear understanding of the interaction between the 2 drugs.

Bradycardia is commonly caused by remifentanil,\[^{22,23}\] probably because of vagal or chronotropic effects. However, the exact mechanism remains unclear.\[^{25,26}\] In the present study, HR did not decrease until propofol was administered in Groups P and PR, although it decreased after the administration of propofol. In Group PR in particular, HR decreased more sharply compared with that in Group P, suggesting that the chronotropic effects of the 2 drugs are synergistic. In contrast, in Group PMR, HR decreased from the early stages, before propofol administration. However, there was no significant difference in HR between Groups PMR and PR at 2 minutes after propofol administration. This was probably caused by blunting of the HR decrease due to incomplete anxiolysis in the early induction period in Group PR.\[^{7}\]

This study has several limitations. First, because endotracheal intubation requires a much higher dose of anesthetic compared with the dose required for loss of consciousness, we used an inhalation agent and muscle relaxants after loss of consciousness to obtain deeper analgesia and muscle relaxation for intubation. Therefore, the response to stimuli such as tracheal intubation and hemodynamic changes during surgery could not be investigated. Second, relatively healthy adult patients were enrolled in our study. Because patients may have different sensitivity to the drugs by their age, the result of this study may not be well applicable to the elderly. Considering that the hemodynamic changes can be more devastating in elderly patients, further research on elderly patients seems necessary.

5. Conclusions

The effective dose of propofol for loss of consciousness could be decreased by 21% and 47% when remifentanil pretreatment was used without and with midazolam, respectively. However, the decrease in blood pressure was greater with pretreatment than sole propofol use. These findings suggest that the combination of remifentanil with or without midazolam may have no benefit on hemodynamic stability during induction using propofol.

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