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Effect of remifentanil and midazolam on ED_{95} of propofol for loss of consciousness in elderly patients

A randomized, clinical trial

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Abstract

Background: Older people are more vulnerable to hemodynamic instability caused by propofol due to their decreased initial distribution volume and increased sensitivity to propofol. Midazolam or remifentanil can often be coadministered because of their synergistic or additive effects with propofol as well as amnesic properties and the blockade of sympathetic stimulation. However, no study has confirmed the appropriate dose of propofol for loss of consciousness in aged patients when administered with other drugs, including opioids or benzodiazepines.

Methods: Patients >65 years scheduled for general anesthesia were enrolled. 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 before propofol, and those in group PMR (propofol–midazolam–remifentanil) received remifentanil and midazolam before propofol. After propofol administration, loss of both 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: In total, 120 patients were randomized into the 3 groups (n = 40). The 95% effective dose of propofol for loss of consciousness was 1.13, 0.87, and 0.72 mg/kg in groups P, PR, and PMR, respectively. The mean blood pressure (MBP) in group PMR was more significantly decreased before propofol injection ($P = .041$) as well as 2 minutes ($P = .005$) and 3 minutes after propofol administration ($P < .001$), compared with group P, but there were no intergroup differences at other time points.

Conclusions: The effective dose of propofol for loss of consciousness in elderly patients could be decreased by 23% and 36% when remifentanil pretreatment was used without and with midazolam, respectively. However, the decrease in MBP was greater with remifentanil and midazolam pretreatment than with propofol alone. These findings suggest that pretreatment with midazolam for propofol infusions with remifentanil in elderly patients should be cautiously used, due to hemodynamic instability during induction.

Abbreviations: ED_{95} = 95% effective dose, HR = heart rate, MBP = mean blood pressure, PAVA = pooled adjacent violators algorithm.

Keywords: effective dose, elderly, midazolam, propofol, remifentanil

1. Introduction

Propofol, a hypnotic agent, can provide quick and smooth induction when used for general anesthesia. It also has a bronchodilating effect and prevents postoperative nausea and vomiting.[1] These advantages lead many anesthesiologists to select propofol as an induction agent. However, it is well known that propofol shows dose-dependent hemodynamic instability, such as hypotension and bradycardia, during induction or bolus administration.[2] The hemodynamic instability is due to dose-dependent decreased systemic vascular resistance and myocardial contractility.[3,4] In particular, in elderly patients or volume-depleted patients, the hemodynamic instability becomes more dramatic. Anesthesiologists, therefore, have to be cautious when selecting the propofol dose for induction in such patients, and the minimal dose of propofol that provides sufficient sedation for most patients has to be administered.

Some trials have been conducted to minimize the propofol dose for the induction of hemodynamic susceptible patients. Coinduction with other analgesics or benzodiazepines can lead to additive or synergistic effects and can thus reduce propofol requirements. It can also decrease the hemodynamic change during the induction period.[5] However, no study has confirmed the appropriate dose of propofol for loss of consciousness in aged patients when administered with other drugs like opioids or benzodiazepines. Therefore, we designed this study to estimate

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the 95% effective dose (ED_{95}) of propofol when patients are pretreated with usual doses of remifentanil or remifentanil with midazolam, and to investigate whether remifentanil and midazolam pretreatment can reduce hemodynamic instability during propofol induction.

2. Methods

This study protocol was approved by the Institutional Review Board of Gangnam Severance Hospital (approval no.: 3-2015-0222) and registered at clinicaltrial.gov (NCT02818387). Patients >65 years scheduled for general anesthesia were considered eligible. Patients with an American Society of Anesthesiologists physical status ≥3; who were allergic to propofol, remifentanil, or midazolam; whose body mass index was ≤20 or ≥30 (kg/m^2); or who were taking hypnotics or antianxiety agents were excluded from the study. Patient who could not read or write or who could not understand the procedure or the consent procedure were also excluded. Written informed consent was obtained from all participants.

2.1. Study protocol

In total, 120 patients were enrolled and divided into 3 groups using a computer-generated randomization table. Before the transfer to the operation room, a 20-gauge intravenous catheter was inserted at the patient's basilic vein and 5 mL/kg of lactated Ringer's solution was infused before the induction. Intravenous glycopyrrolate (0.1 mg) was administered as premedication to all patients. In the operating room, the monitoring included pulse oximetry, noninvasive blood pressure, an electrocardiogram, and mult-gas analysis. Each patient received intravenous propofol after 5 minutes of preoxygenation. After the monitoring, group P (propofol) was induced only with propofol. In group PR (propofol–remifentanil), 0.125 μg/kg/min of remifentanil was continuously infused from the start of preoxygenation until 3 minutes after propofol administration. In group PMR (propofol–midazolam–remifentanil), intravenous midazolam 0.025 mg/kg was additionally administered 1 minute after preoxygenation. Due to concerns about increased brain sensitivity and decreased drug clearance in elderly patients, the initial propofol dose was determined to be 0.5 mg/kg, and the doses of remifentanil and midazolam were half of the doses reported in a prior study by Koh et al that was performed in healthy young patients.[6,7] After the predetermined dose of propofol was administered, the loss of the eyelash reflex and verbal response was assessed for 3 minutes. Induction success was represented by loss of both the eyelash reflex and verbal response. All other cases were considered failures.

The dose of propofol was determined before the induction according to the up-and-down method using a biased coin design which was described by Durham et al.[6,8] If induction failed in one patient, the propofol dose for the next patient was increased by 0.125 mg/kg. If induction was successful in one patient, the dose for the next patient was determined with 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 0.125 mg/kg, and the same dose was administered with a probability of 18/19. Mean blood pressure (MBP), heart rate (HR), and oxygen saturation were measured at baseline, immediately before propofol injection, and 1, 2, and 3 minutes after propofol injection. Any adverse effects were monitored and recorded.

2.2. Statistical analysis

A minimum of 40 subjects were required, according to the methods of Durham et al.[7] We therefore enrolled 40 patients in each group. Statistical analyses were performed using the Statistical Package for Social Sciences (ver. 20.0 for Windows; SPSS Inc., Chicago, IL) and R for Windows (R ver. 3.2.0). The pooled adjacent violators algorithm (PAVA) was used to predict the effective dose of propofol for the successful loss of consciousness in 95% of patients (ED_{95}), and bootstrapping was used to estimate the 95% confidence intervals. ANOVA and a linear mixed model were used to analyze the demographic data and hemodynamic changes in each group. A $P < .05$ was considered statistically significant.

3. Results

From the total of 126 patients, 6 refused to participate in the study. A total of 120 patients were equally divided into 3 groups. No demographic differences in age, height, weight, and comorbidity (Table 1) were observed. Figure 1 depicts the allocation sequence for each group according to the biased coin design. Starting from propofol 0.5 mg/kg, the propofol dose for the next patient was increased by 0.125 mg/kg if the induction was failed. If induction was successful, the dose for the next patient was decreased by 0.125 mg/kg with a probability of 1/19, and the same dose was administered with a probability of 18/19. The pooled adjacent violators algorithm-adjusted success rate in each group is shown in Figure 2. The dose required for loss of consciousness during induction was higher in group P, followed in group PR and then group PMR. The ED_{95} of propofol for loss of consciousness was 1.13, 0.87, and 0.72 mg/kg in groups P, PR, and PMR, respectively (Table 2).

Figure 3 shows the hemodynamic profiles. In all groups, the MBP was significantly decreased at 1, 2, and 3 minutes after

Table 1

Demographic characteristics of the patients in each group.

	P (n = 40)	PR (n = 40)	PMR (n = 40)	*P*
Age, y	72.3 ± 4.86	70.5 ± 4.07	71.43 ± 4.13	.187
Height, cm	157.5 ± 8.50	159.57 ± 8.68	157.37 ± 9.29	.460
Weight, kg	60.55 ± 8.63	61.58 ± 8.68	61.06 ± 8.49	.864
Comorbidities				
Hypertension	22 (55%)	23 (57.5%)	20 (50%)	.791
Diabetes mellitus	7 (17.5%)	6 (15%)	8 (20%)	.841

Values are mean ± standard deviation or the patient number (percentage). Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.125 μg/kg/min) before propofol. Group PMR: patients who received both midazolam (0.025 mg/kg) and remifentanil before propofol.

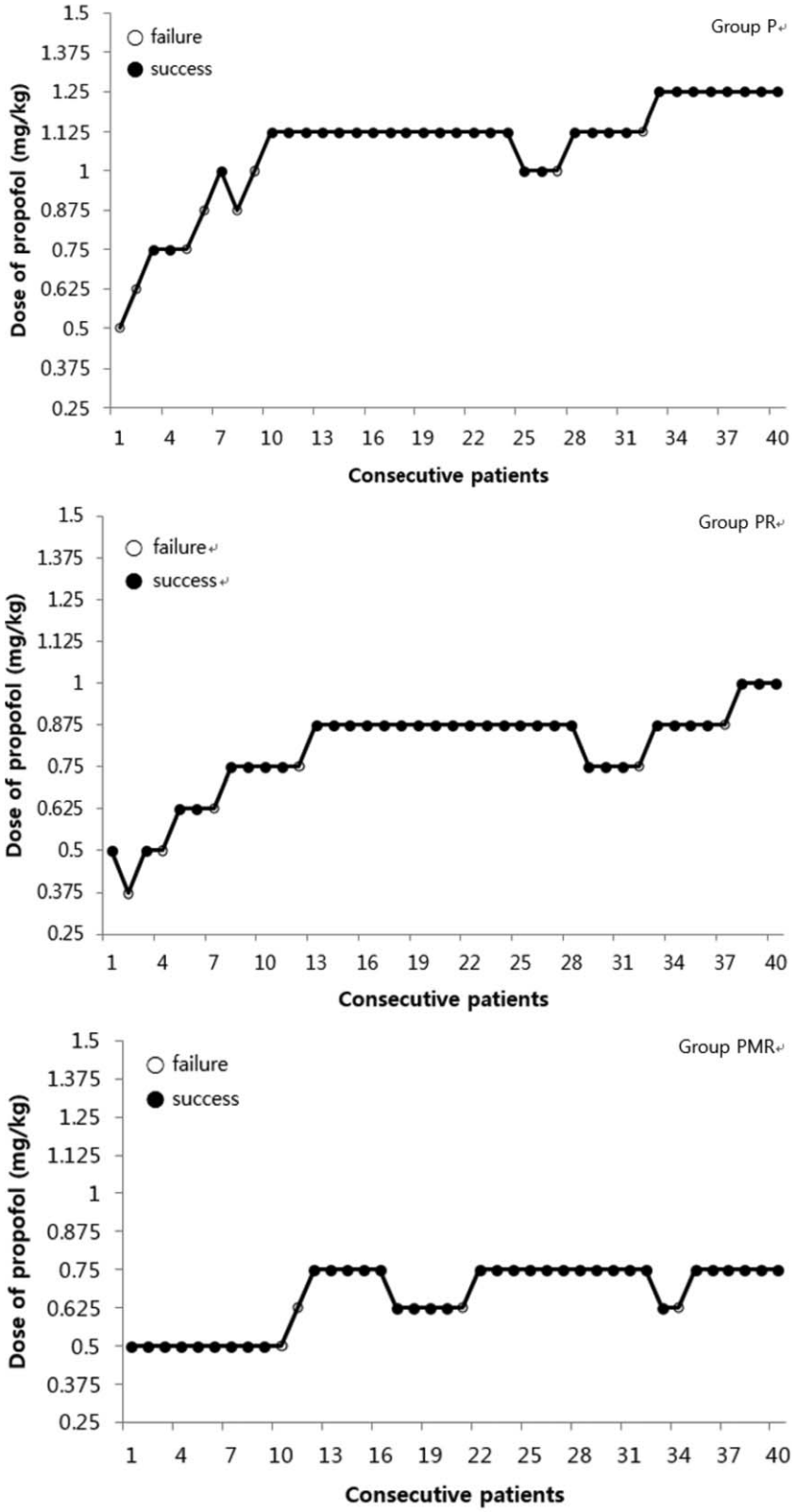

Figure 1. Assessment of success or failure of anesthesia induction by a predetermined bolus dose of propofol determined for consecutive patients using a modified biased coin design in each group. Induction success (loss of consciousness) is indicated by solid circles, and induction failure (no loss of consciousness) is indicated by open circles. Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.125 μg/kg/min) before propofol. Group PMR: patients who received both midazolam (0.025 mg/kg) and remifentanil before propofol.

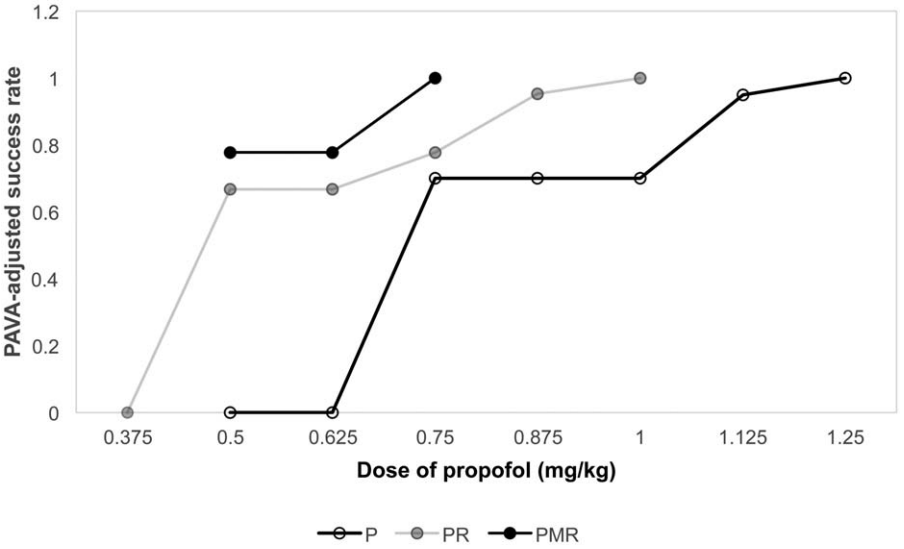

Figure 2. The pooled adjacent violators algorithm (PAVA)-adjusted success rate according to dose level in each group. Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.125 μg/kg/min) before propofol. Group PMR: patients who received both midazolam (0.025 mg/kg) and remifentanil before propofol.

propofol administration, compared with baseline ($P<.001$ for all groups at each time). However, the MBP was also decreased before propofol administration in group PR ($P=.001$) and group PMR ($P<.001$), respectively. The MBP in group PMR, compared with Group P, was significantly decreased before propofol injection ($P=.041$) as well as 2 minutes ($P=.005$) and 3 minutes after propofol administration ($P<.001$), but there were no intergroup differences at other time points.

In all groups, the HR was significantly decreased 1 minute ($P=.045$ in group P, $P<.001$ in groups PR and PMR), 2 minutes ($P=.001$ in group P, $P<.001$ in groups PR and PMR), and 3 minutes ($P<.001$ in all groups) after propofol administration, compared with baseline. Before propofol administration, only the HR in group PMR showed a significant decrease compared with baseline ($P=.001$). However, there were no intergroup differences in HR at any time points. No adverse effects related to the administered drugs were recorded.

4. Discussion

In this study, we investigated the ED_{95} of propofol with no pretreatment (group P), remifentanil pretreatment (group PR), and remifentanil plus midazolam pretreatment (group PMR) in elderly patients for loss of consciousness during the induction of general anesthesia. Our results show that the required dose of propofol was reduced to 22.4% with using remifentanil, and 35.8% with remifentanil with midazolam. However, the MBP decreased significantly after pretreatment with remifentanil and midazolam, compared with the group that received only propofol.

Table 2

Comparison of the 95% effective dose (ED_{95}) of propofol for loss of consciousness using isotonic regression in each group.

	P (n = 40)	PR (n = 40)	PMR (n = 40)
ED_{95}, mg/kg	1.13 (1.11–1.24)	0.87 (0.86–0.98)	0.72 (0.7–0.73)

Values are means (95% confidence intervals). Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.125 μg/kg/min) before propofol. Group PMR: patients who received both midazolam (0.025 mg/kg) and remifentanil before propofol. ED_{95} = 95% effective dose.

Nowadays, elderly patients constitute a large proportion of the surgical population. Anesthesiologists are often faced with the need for tailoring anesthesia techniques, to account for geriatric physiology. Unfortunately, geriatric-specific guidelines on anesthesia do not exist, and an anesthesiologist may thus try to modify techniques based on a nonscientific impression of what is best for the patient. Furthermore, it has been reported that elderly patients commonly receive greater-than-recommended doses (1–1.5 mg/kg) of propofol for the induction of general anesthesia.[9] In our result, the ED_{95} of propofol for loss of consciousness in elderly patients (>65 years) was 1.13 mg/kg, which is 35% lower than that reported for 20- to 50-year-old patients (1.74 mg/kg) in a previous study.[7] Our findings are similar to those of Olmos et al, showing a 37% reduction in the effect-site concentration of propofol for hypnosis in patients >60 years compared with those <40 years.[10] Our results confirm the guideline for minimal administration of propofol, as higher doses can be unnecessarily excessive in elderly patients. Older people are more vulnerable to hemodynamic instability caused by propofol, due to a decreased initial distribution volume and increased sensitivity to propofol.[9,11,12] It has been reported that postinduction hypotension was associated with increased mortality, and that intraoperative hypotension caused reinfarction in 20% of patients with myocardial infarction.[13,14] Concerns about hemodynamic depression in old patients lead anesthesiologists to avoid using propofol alone for induction and to use combinations with other drugs. In addition, midazolam and remifentanil are often required during the induction period because of their strong amnesic property and the blockade of sympathetic stimulation induced by laryngoscopy and intubation. Synergistic effects of propofol and opioids, benzodiazepines, or both have been reported.[10,15–18] However, we are not aware of recommendations regarding the appropriate dose of propofol during induction when opioids or benzodiazepines are coadministered in elderly patients. Opioids are also commonly used with

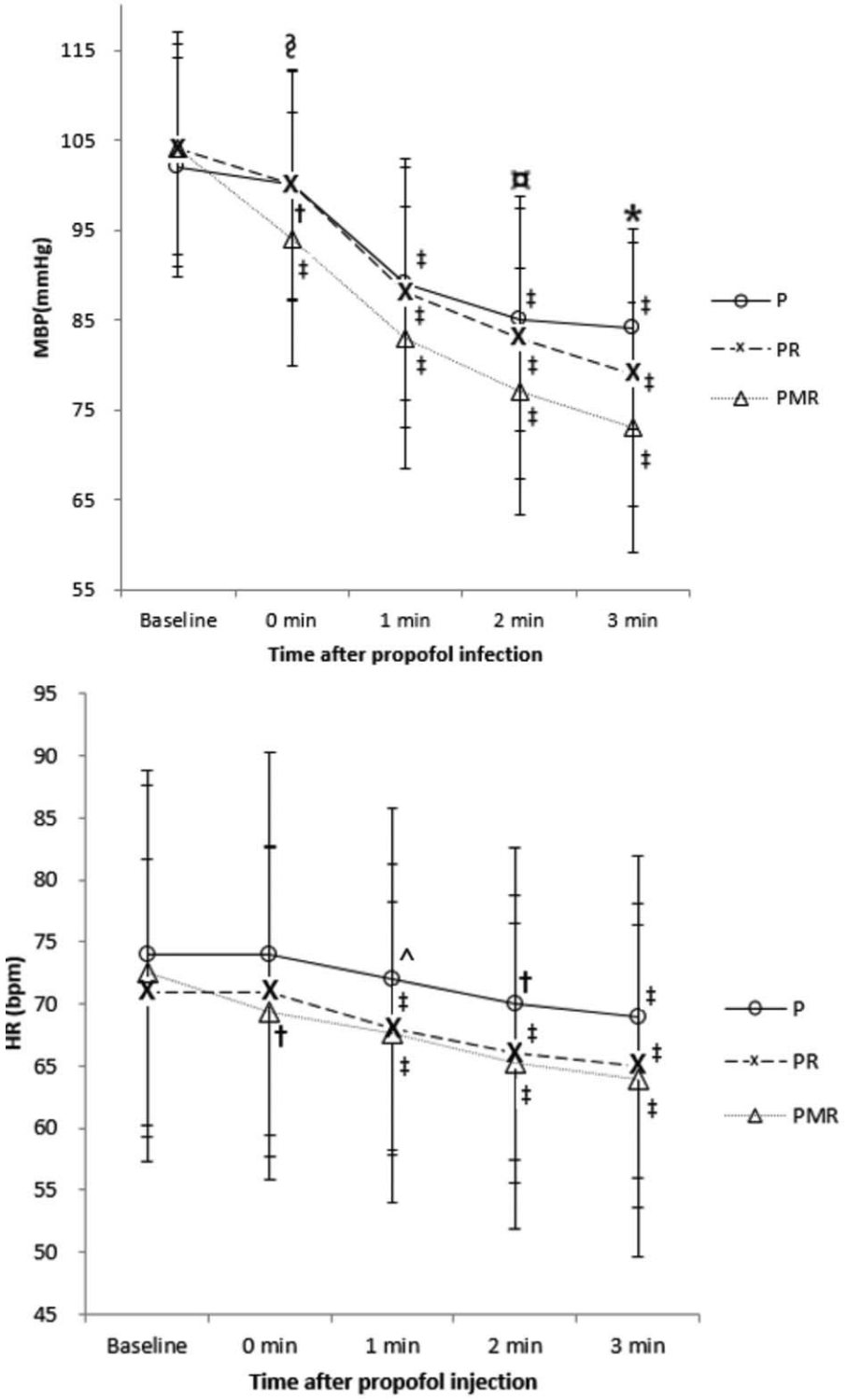

Figure 3. Mean blood pressure and heart rate values at baseline, before propofol administration, and 1, 2, and 3 minutes after propofol administration in each group. Values are presented as the mean ± standard deviation. MBP = mean blood pressure, HR = heart rate, Baseline = the patient is at rest, 0 min = before injection of designated dose of propofol, 1, 2, and 3 minutes = 1, 2, and 3 minutes after propofol injection, Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.125 μg/kg/min) before propofol. Group PMR: patients who received both midazolam (0.025 mg/kg) and remifentanil before propofol. §Significantly decreased compared with groups P and PMR ($P<.05$), ¤ significantly decreased compared with groups P and PMR ($P<.01$). *Significantly decreased compared with groups P and PMR ($P<.001$). ^Significantly decreased compared with baseline ($P<.05$). †Significantly decreased compared with baseline ($P<.01$). ‡Significantly decreased compared with baseline ($P<.001$).

propofol for the induction of general anesthesia because propofol does not have an analgesic effect. Opioids can help anesthesiologists reduce the propofol dose because they lead to synergistic effects in hypnosis.[19] However, compared with the synergistic effects of propofol and benzodiazepines, the synergism between propofol and opioids has been reported to be rather weak [16,20] and the hypnotic synergism between propofol and opiates shows a ceiling effect.[15] With remifentanil pretreatment, the ED_{95} of propofol (0.87 mg/kg) was reduced by 23%, in comparison to propofol alone (1.13 mg/kg), in our results. The reduction of the dose of propofol after pretreatment with remifentanil in elderly patients is comparable to that reported for young patients (21% dose reduction of propofol).[7] We cannot estimate the exact drug interaction of propofol and remifentanil because an isobolographic analysis was not conducted in our study. However, our results suggest that propofol doses ≥1.0 mg/kg are more than necessary for loss of consciousness in the elderly (>65 years) when remifentanil pretreatment is coadministered during the induction period.

Midazolam is a frequently selected benzodiazepine because of its short half-life, pH-dependent solubility, and short elimination half-life.[21,22] Midazolam has a great advantage in eliminating unpleasant perioperative memories because of its strong anterograde amnesic properties. Furthermore, in addition to its anxiolytic effect, intravenous preadministration of midazolam has been reported to reduce postoperative nausea and vomiting and increase patient satisfaction.[23] We expected coinduction with midazolam and remifentanil to lead to better hemodynamic stability because of a higher reduction of the propofol dose resulting from synergistic or additive effects of midazolam and propofol, compared with propofol alone. However, the reduction of the propofol requirement for hypnosis in elderly patients after pretreatment with midazolam and remifentanil might be smaller than what we had expected. The exact mechanism is not well understood; however, Vinik et al found that the propofol–midazolam–alfentanil interaction resulted in profound hypnotic synergism that was, however, not significantly different from that of the binary propofol–alfentanil combination.[17,20] This implies that the 3-drug combination did not produce as much sedation as expected from the combined doses of the individual agents and the pairwise interactions.[20] Pretreatment with midazolam and remifentanil led to a significant decrease in MBP, compared with propofol alone, possibly caused by the midazolam-induced alteration of propofol pharmacokinetics. When combined with midazolam, propofol concentrations reach higher levels than when propofol is administered alone.[24] Although we did not measure propofol concentrations and do not know the propofol pharmacokinetics, it seems that pretreatment with midazolam does not reduce propofol requirements enough to cause more stable blood pressure in the elderly. Our results suggest that during induction with propofol with remifentanil pretreatment in elderly patients, prior administration of midazolam should be carefully considered because it may lead to worsen hemodynamic instability.

Bradycardia is commonly caused by opioids,[25,26] presumably because of vagal or chronotropic effects. In the PMR group, the HR decreased even before propofol administration, whereas it did not decrease until propofol was administered in groups P and PR. In addition, the PR and PMR groups showed a higher tendency toward a decrease in HR than the group P, although there was no significant difference in HR at any time point between the groups. It may be advisable to be careful with midazolam or remifentanil pretreatment in older patients with marked or severe bradycardia or hemodynamic instability, even if most elderly patients have no problem.

This study has several limitations. First, we did not analyze hemodynamic parameters during the postinduction period because the study was not designed for this purpose; additional doses of propofol administered to the patients were declared as "failure." Moreover, we used an inhalation agent after loss of consciousness to obtain deeper analgesia for endotracheal intubation. Second, although patients with an American Society of Anesthesiologists physical status ≥4 were excluded, elderly patients with comorbidities, such as hypertension or diabetes, were heterogeneously included, which might have resulted in variations in hemodynamic responses to the drugs during the study period.

In conclusion, the effective dose of propofol for loss of consciousness in elderly patients could be decreased by 23% and 36% when remifentanil pretreatment was used without and with midazolam, respectively. However, the decrease in blood pressure was greater with remifentanil and midazolam pretreatment than with propofol alone. These findings suggest that pretreatment with midazolam should be cautiously used because of the hemodynamic instability during induction with propofol with remifentanil infusion in elderly patients.

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Writing – original draft: Ann Hee You, Ji Young Kim, Dong Woo Han.
Writing – review and editing: Ann Hee You, Ji Young Kim, Dong Woo Han.

References

[1] Shinn HK, Lee MH, Moon SY, et al. Post-operative nausea and vomiting after gynecologic laparoscopic surgery: comparison between propofol and sevoflurane. Korean J Anesthesiol 2011;60:36–40.
[2] Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3–9.
[3] Gragasin FS, Davidge ST. The effects of propofol on vascular function in mesenteric arteries of the aging rat. Am J Physiol Heart Circ Physiol 2009;297:H466–74.
[4] Memtsoudis SG, Heerdt PM. Autonomic mechanisms in the age-related hypotensive effect of propofol. Anesth Analg 2005;100:111–5.
[5] Cressey D, Claydon P, Bhaskaran N, et al. Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. Anaesthesia 2001;56:108–13.
[6] Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a precis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology 2007;107:144–52.
[7] Koh JC, Park J, Kim NY, et al. 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. Medicine 2017;96:e9164.
[8] Durham SD, Flournoy N, Rosenberger WF. A random walk rule for phase I clinical trials. Biometrics 1997;745–60.

[9] Phillips AT, Deiner S, Lin HM, et al. Propofol use in the elderly population: prevalence of overdose and association with 30-day mortality. Clin Ther 2015;37:2676–85.
[10] Olmos M, Ballester J, Vidarte M, et al. The combined effect of age and premedication on the propofol requirements for induction by target-controlled infusion. Anesth Analg 2000;90:1157–61.
[11] Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502–16.
[12] Arden JR, Holley FO, Stanski DR. Increased sensitivity to etomidate in the elderly: initial distribution versus altered brain response. Anesthesiology 1986;65:19–27.
[13] Charlson ME, MacKenzie CR, Gold JP, et al. The preoperative and intraoperative hemodynamic predictors of postoperative myocardial infarction or ischemia in patients undergoing noncardiac surgery. Ann Surg 1989;210:637.
[14] Reich DL, Hossain S, Krol M, et al. Predictors of hypotension after induction of general anesthesia. Anesth Analg 2005;101:622–8.
[15] Smith C, McEwan AI, Jhaveri R, et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. Anesthesiology 1994;81:820–8.
[16] McClune S, McKay A, Wright P, et al. Synergistic interaction between midazolam and propofol. Br J Anaesth 1992;69:240–5.
[17] Vinik H, Bradley JE, Kissin I. Triple anesthetic combination: propofol-midazolam-alfentanil. Anesth Analg 1994;78:354–8.
[18] Ang S, Cheong K, Ng T. Alfentanil co-induction for laryngeal mask insertion. Anaesth Intensive Care 1999;27:175.
[19] Singh SA, Prakash K, Sharma S, et al. Comparison of propofol alone and in combination with ketamine or fentanyl for sedation in endoscopic ultrasonography. Korean J Anesthesiol 2018;71:43–7.
[20] Short T, Chui P. Propofol and midazolam act synergistically in combination. Br J Anaesth 1991;67:539–45.
[21] Allonen H, Ziegler G, Klotz U. Midazolam kinetics. Clin Pharmacol Ther 1981;30:653–61.
[22] Greenblatt DJ, Divoll M, Abernethy DR, et al. Pharmacokinetics of benzodiazepine hypnotics. Pharmacology 1983;27:70–5.
[23] Bauer KP, Dom PM, Ramirez AM, et al. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth 2004;16: 177–83.
[24] Vuyk J, Lichtenbelt BJ, Olofsen E, et al. Mixed-effects modeling of the influence of midazolam on propofol pharmacokinetics. Anesth Analg 2009;108:1522–30.
[25] Masjedi M, Zand F, Kazemi AP, et al. Prophylactic effect of ephedrine to reduce hemodynamic changes associated with anesthesia induction with propofol and remifentanil. J Anaesthesiol Clin Pharmacol 2014;30:217–21.
[26] Hayashi K, Tanaka A. Effect-site concentrations of remifentanil causing bradycardia in hypnotic and non-hypnotic patients. J Clin Monit Comput 2016;30:919–24.