Clinical Trial/Experimental Study

Medicine®

OPEN

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

Jae Chul Koh, MD[a], Juyeon Park, MD[b], Na Young Kim, MD, PhD[c], Ann Hee You, MD, PhD[c], Seo Hee Ko, MD[c], Dong Woo Han, MD, PhD[c,*]

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, ED_{95} = 95% effective dose, HR = heart rate, MBP = mean blood pressure, SpO_2 = oxygen saturation.

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

Editor: Hiroyuki Kinoshita.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest to disclose.

[a] Department of Anesthesiology and Pain Medicine, Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea, [b] Department of Anesthesia and Pain Medicine, Pusan National University, Yangsan Hospital, Yangsan, [c] Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, South Korea.

[*] Correspondence: Dong Woo Han, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Republic of Korea (e-mail: hanesth@yuhs.ac).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc.
This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:49(e9164)

Received: 29 June 2017 / Received in final form: 31 October 2017 / Accepted: 16 November 2017

http://dx.doi.org/10.1097/MD.0000000000009164

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.[1,2] 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.[3–6] Midazolam is a benzodiazepine commonly used as a pretreatment agent to decrease anxiety and improve patient satisfaction levels.[7] Remifentanil is an opioid used for intraoperative pain control. Pretreatment with remifentanil can decrease injection pain[8] and provide hemodynamic stability during the induction period.[9,10] 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 (ED_{95}) 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 ≤ 20 or ≥ 30 kg/m^2 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 5 mL/kg of 0.9% normal saline was infused before the induction. Intravenous glycopyrrolate 0.2 mg 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 5 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 0.25 μg/kg/min was intravenously infused from the start of preoxygenation until 2 minutes after propofol administration. In Group PMR, intravenous midazolam 0.05 μg/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.[11,12] The initial dose was set as 1.0 mg/kg for each group; this was the least successful hypnotic dose of propofol in a previous study.[4] If induction failed in 1 patient, the dose for the next patient was increased by 0.25 mg/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 0.25 mg/kg, and the same dose was administered with a probability of 18/19.

The mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO_2) 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.[11] 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 (ED_{95}), 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 ED_{95}. 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 ED_{95} of propofol was 1.74, 1.38, and 0.92 mg/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).

Table 1

Demographic characteristics of patients in each group.

Group	P (n = 40)	PR (n = 40)	PMR (n = 40)	*P* value
Age	37.9 ± 8.7	35.7 ± 7.9	38.3 ± 8.9	.83
Height, cm	160.8 ± 5.7	161.1 ± 5.0	161.0 ± 4.9	.91
Weight, kg	57.5 ± 7.4	56.6 ± 6.5	57.4 ± 7.7	.91
BMI, kg/m^2	22.3 ± 3.0	21.8 ± 2.6	22.2 ± 3.1	.86

Values are expressed as means ± standard deviations.
Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.25 μg/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05 μg/kg) and remifentanil prior to propofol.
BMI = body mass index.

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.

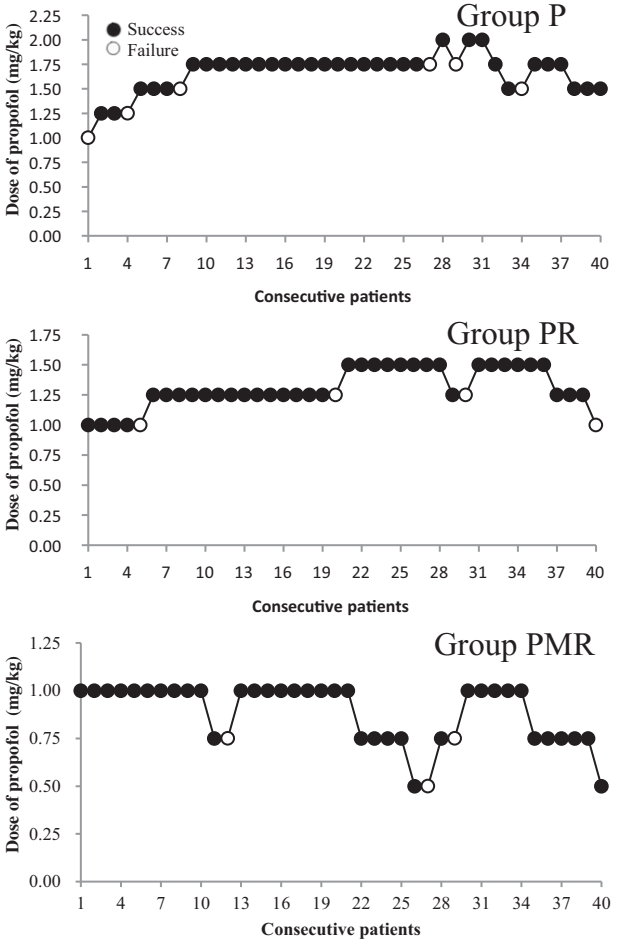

Figure 1. Assessment of success or failure of anesthesia induction by a predetermined bolus dose of propofol determined for consecutive patients using a modified biased coin design in each group. Induction success (loss of consciousness) is indicated by solid circles, and induction failure (no loss of consciousness) is indicated by open circles. Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.25 μg/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05 μg/kg) and remifentanil prior to propofol.

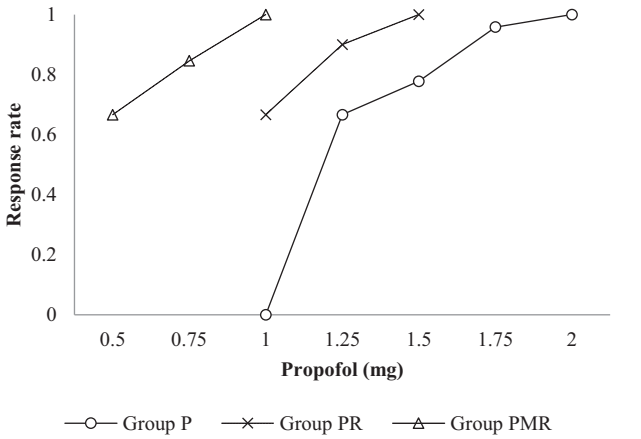

Figure 2. The pooled adjacent violators algorithm response rate for each group. For the higher success rate for loss of consciousness, Group P required higher dose of propofol, followed by Group PR and Group PMR. Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.25 μg/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05 μg/kg) and remifentanil prior to propofol.

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 ED_{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

Table 2

The 95% effective dose of propofol required for loss of consciousness in each group.

Group	ED_{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 (0.25 μg/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05 μg/kg) and remifentanil prior to propofol.
CI = confidence interval, ED_{95} = 95% effective dose.

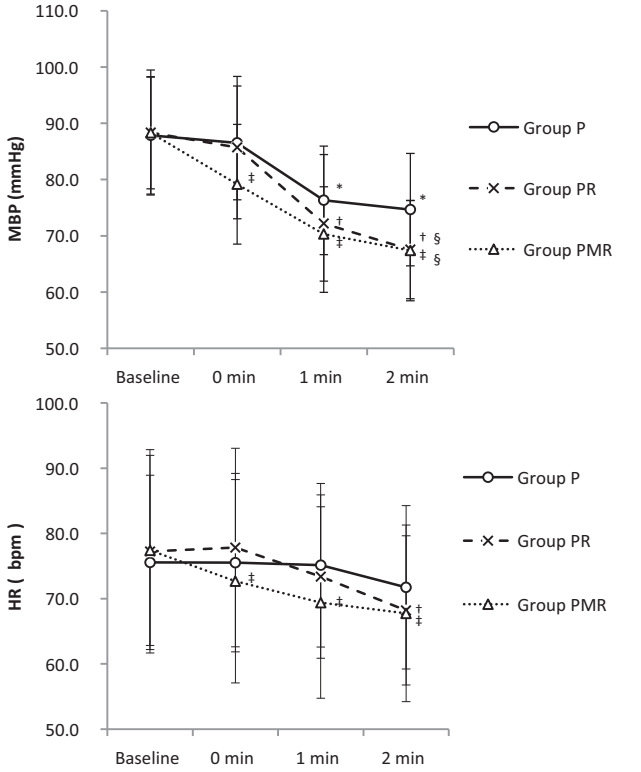

Figure 3. Mean blood pressure and heart rate values at baseline, before propofol administration, and 1 and 2 minutes after propofol administration in each group. Values are presented as mean ± standard deviation. MBP was more significantly decreased at Group PR and PMR compared with Group P at 2 minutes after propofol administration ($P = .02$ and $P = .01$, respectively). There were no intergroup differences in HR at each time point. *, †, ‡: Significantly decreased compared with baseline values in Group P, Group PR, and Group PMR, respectively ($P < .05$). §: Significantly decreased compared with Group P. MBP = mean blood pressure, HR = heart rate, 0 min, 1 min, 2 min = before and 1 and 2 minutes after propofol administration, respectively. Group P: patients who received only propofol for loss of consciousness. Group PR: patients who received remifentanil (0.25 g/kg/min) prior to propofol. Group PMR: patients who received both midazolam (0.05 g/kg) and remifentanil prior to propofol.

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.[16] 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.[22] 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,[22,25] 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.

Acknowledgment

The authors thank Ms Jung Hwa Hong for her statistical analysis of the study data.

References

[1] Fassl J, High KM, Stephenson ER, et al. The intravenous anesthetic propofol inhibits human L-type calcium channels by enhancing voltage-dependent inactivation. J Clin Pharmacol 2011;51:719–30.

[2] Robinson BJ, Ebert TJ, O'Brien TJ, et al. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? Anesthesiology 1997;86:64–72.

[3] Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004;100:1353–72.

[4] Cressey DM, Claydon P, Bhaskaran NC, 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.

[5] Goyagi T, Tanaka M, Nishikawa T. Fentanyl decreases propofol requirement for laryngeal mask airway insertion. Acta Anaesthesiol Scand 2003;47:771–4.

[6] Milne SE, Kenny GN, Schraag S. Propofol sparing effect of remifentanil using closed-loop anaesthesia. Br J Anaesth 2003;90:623–9.

[7] Bauer KP, Dom PM, Ramirez AM, et al. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth 2004;16:177–83.

[8] Lee SH, Lee SE, Chung S, et al. Impact of time interval between remifentanil and propofol on propofol injection pain. J Clin Anesth 2016;34:510–5.

[9] Goo EK, Lee JS, Koh JC. The optimal exhaled concentration of sevoflurane for intubation without neuromuscular blockade using clinical bolus doses of remifentanil: a randomized controlled trial. Medicine (Baltimore) 2017;96:e6235.

[10] Hall AP, Thompson JP, Leslie NA, et al. Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation. Br J Anaesth 2000;84:100–2.

[11] Durham SD, Flournoy N, Rosenberger WF. A random walk rule for phase I clinical trials. Biometrics 1997;53:745–60.

[12] 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.

[13] Liu X, Pan Z, Su D, et al. Remifentanil ameliorates liver ischemia-reperfusion injury through inhibition of interleukin-18 signaling. Transplantation 2015;99:2109–17.

[14] Sayan-Ozacmak H, Ozacmak VH, Turan I, et al. Pretreatment with remifentanil protects against the reduced-intestinal contractility related to the ischemia and reperfusion injury in rat. Braz J Anesthesiol 2015;65:483–90.

[15] Zhang Y, Li YW, Wang YX, et al. Remifentanil preconditioning alleviating brain damage of cerebral ischemia reperfusion rats by regulating the JNK signal pathway and TNF-alpha/TNFR1 signal pathway. Mol Biol Rep 2013;40:6997–7006.

[16] Short TG, Hannam JA, Laurent S, et al. Refining target-controlled infusion: an assessment of pharmacodynamic target-controlled infusion of propofol and remifentanil using a response surface model of their combined effects on bispectral index. Anesth Analg 2016;122:90–7.

[17] McCleane GJ, Fogarty DF, Watters CH. Factors that influence the induction dose of propofol. Anaesthesia 1991;46:59–61.

[18] Cimen NK, Kosem B, Cimen T, et al. Effects of remifentanil, nitroglycerin, and sevoflurane on the corrected QT and Tp-e intervals during controlled hypotensive anesthesia. J Clin Anesth 2016;33:365–72.

[19] Sajedi P, Rahimian A, Khalili G. Comparative evaluation between two methods of induced hypotension with infusion of Remifentanil and Labetalol during sinus endoscopy. J Res Pharm Pract 2016;5:264–71.

[20] Noseir RK, Ficke DJ, Kundu A, et al. Sympathetic and vascular consequences from remifentanil in humans. Anesth Analg 2003;96:1645–50.

[21] Baker KZ, Ostapkovich N, Sisti MB, et al. Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. J Neurosurg Anesthesiol 1997;9:134–40.

[22] 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.

[23] Frolich MA, Arabshahi A, Katholi C, et al. Hemodynamic characteristics of midazolam, propofol, and dexmedetomidine in healthy volunteers. J Clin Anesth 2011;23:218–23.

[24] Arpaci AH, Bozkirli F. Comparison of sedation effectiveness of remifentanil-dexmedetomidine and remifentanil-midazolam combinations and their effects on postoperative cognitive functions in cystoscopies: a randomized clinical trial. J Res Med Sci 2013;18:107–14.

[25] 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.

[26] Wujtewicz MA, Hasak L, Twardowski P, et al. Evaluation of the relationship between baseline autonomic tone and the vagotonic effect of a bolus dose of remifentanil. Anaesthesia 2016;71:823–8.