



## ANESTHESIA INDUCTION WITH MIDAZOLAM AND PROPOFOL AFTER MIDAZOLAM PREMEDICATION: DOSE FINDING OF THE COMBINATION

Tomoki Nishiyama\*

Department of Anesthesiology, Kamakura Hospital, 3-1-8, Hase, Kamakura-shi, Kanagawa, 248-0016, Japan.

\*Corresponding Author: Dr. Tomoki Nishiyama

Department of Anesthesiology, Kamakura Hospital, 3-1-8, Hase, Kamakura-shi, Kanagawa, 248-0016, Japan.

Article Received on 10/06/2019

Article Revised on 30/06/2019

Article Accepted on 21/07/2019

### ABSTRACT

This study was performed to investigate optimal doses of midazolam and propofol in combination for induction of anesthesia. One hundred and eighty patients aged 30 to 70 years for general anesthesia were equally divided into 6 groups. Midazolam 0.05 mg/kg was intramuscularly administered 15 minutes before entering the operating room. Anesthesia was induced with midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.20 mg/kg with vecuronium 0.01 mg/kg, and 2 minutes later, propofol infusion was started at 200 mg/min. Eyelash reflex and verbal response were checked every 10 seconds and when both disappeared, propofol infusion was stopped, then vecuronium 0.14 mg/kg was administered for oro-tracheal intubation. The total dose of propofol of the patients whose systolic blood pressure one minute after intubation was within  $\pm 20\%$  of pre-induction value was judged as an adequate dose. The dose of propofol judged as adequate was  $2.46 \pm 0.59$ ,  $2.12 \pm 0.47$ ,  $1.85 \pm 0.45$ ,  $1.36 \pm 0.42$ ,  $1.22 \pm 0.53$ , or  $0.82 \pm 0.53$  mg/kg at midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.2 mg/kg, respectively. After premedication with intramuscular midazolam 0.05 mg/kg, midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.2 mg/kg and propofol  $2.46 \pm 0.59$ ,  $2.12 \pm 0.47$ ,  $1.85 \pm 0.45$ ,  $1.36 \pm 0.42$ ,  $1.22 \pm 0.53$ , or  $0.82 \pm 0.53$  mg/kg, respectively could give stable hemodynamics at induction of anesthesia.

**KEYWORDS:** anesthesia induction, propofol, midazolam.

For induction of anesthesia, propofol, barbiturate, or midazolam is usually used. Propofol and barbiturate have a rapid onset but induced marked hemodynamic changes. Midazolam induces stable hemodynamics but has slow onset. Therefore, combination of midazolam with propofol or barbiturate might be useful to induce rapid onset and stable hemodynamics if synergistic interaction is found because they allow the use of smaller doses of each drug and thus potentially decrease side effects. We have already shown that co-induction of anesthesia with midazolam and barbiturate had a benefit to decrease intubation induced hemodynamic changes.<sup>[1]</sup> Some studies showed that midazolam and propofol had synergistic effects.<sup>[2,3]</sup> The doses of propofol required for induction of anesthesia when combined with midazolam have been investigated using many different indicators, such as 50% effective doses (ED50s) for various target, hypnotic dose, response to pain, etc.<sup>[3,4,5]</sup> However, most important might be complete loss of consciousness and hemodynamic stability in all patients. Therefore, this study was performed to investigate optimal doses of midazolam and propofol in combination for induction of anesthesia using loss of consciousness and eyelash reflex as well as changes in blood pressure after intubation as indices.

Premedication has not been used for recent years, but without premedication, many patients showed high blood pressure, tachycardia, arrhythmia, and/or agitation when they come into the operating room. Therefore, anxiolytic premedication is still necessary. The present study was then performed using premedication.

### METHODS

After the approval of the Ethics Committee of the Kamakura Hospital (No.009) and informed consent from the patients, 180 patients aged 30 to 70 years with ASA physical status I or II for general anesthesia were divided into 6 groups of each 30 patients by an envelope method at random. Those who had liver, renal, mental, or severe cardiac diseases, who had allergy to the agents scheduled to use, or habits of hypnotics or analgesics, and who were obese (body mass index > 30) were excluded from the study.

Midazolam 0.05 mg/kg was intramuscularly administered 15 minutes before entering the operating room as our common practice. Anesthesia was induced with midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.20 mg/kg with vecuronium 0.01 mg/kg, and 2 minutes later, propofol infusion at 200 mg/min was started. Eyelash reflex and verbal response were checked every 10

seconds and when both disappeared, propofol infusion was stopped, then vecuronium 0.14 mg/kg was administered. After muscle relaxation was obtained, oro-tracheal intubation was performed. Thereafter, anesthesia was maintained with sevoflurane 2% in 50% oxygen for 10 minutes, then fentanyl 2 - 3 µg/kg was administered before surgery. The patients whose intubation was not success at the first trial were excluded from the study. The total dose of propofol of the patients whose systolic blood pressure one minute after intubation was within  $\pm 20\%$  of pre-induction value was judged as an adequate dose. Blood pressure, heart rate, and Bispectral index (BIS) were recorded till 10 minutes after intubation.

### Statistical analysis

Data were expressed as number of patients or mean  $\pm$  standard deviation. Statistical analysis was performed with factorial analysis of variance (ANOVA) and chi-square test for demographic data, number of patients with adequate blood pressure, and propofol dose. Repeated measures ANOVA followed by Student Neuman-Keuls test was used for blood pressure, heart rate and BIS (StatView 5.0, SAS Institute, Cary NC, USA). The p value less than 0.05 was considered to be statistically significant. Post-hoc power analysis was performed using G Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) with effect size 0.25.

## RESULTS

The power was 0.99. Demographic data were not different among the groups (Table 1).

Table 1. Background of patients

Dose of midazolam (mg/kg)	0.025	0.05	0.075	0.1	0.15	0.2
Age (years)	52 $\pm$ 8	53 $\pm$ 11	54 $\pm$ 8	52 $\pm$ 10	57 $\pm$ 9	51 $\pm$ 12
Gender (male/female)	18/12	14/16	15/15	17/13	16/14	11/19
Body weight (kg)	62 $\pm$ 9	63 $\pm$ 6	63 $\pm$ 7	64 $\pm$ 5	63 $\pm$ 5	62 $\pm$ 6
Height (cm)	166 $\pm$ 4	165 $\pm$ 5	165 $\pm$ 5	166 $\pm$ 5	164 $\pm$ 6	165 $\pm$ 5
Duration of surgery (min)	175 $\pm$ 54	156 $\pm$ 61	173 $\pm$ 55	177 $\pm$ 60	182 $\pm$ 66	154 $\pm$ 46

Mean  $\pm$  standard deviation or number of patients. No significant differences were observed.

All patients were successfully intubated at the first trial. The number of the patients whose blood pressure after intubation met the criteria was shown in the Table 2 (Table 2).

Table 2. Number of patients with postoperative blood pressure in  $\pm 20\%$  of preinduction value

Dose of midazolam (mg/kg)	0.025	0.05	0.075	0.1	0.15	0.2
Number of patients	20	21	22	23	21	22

No significant differences were observed among the groups.

No differences were observed among the groups. Blood pressure significantly decreased after induction and increased after intubation, but no differences were found among the groups (Fig. 1).

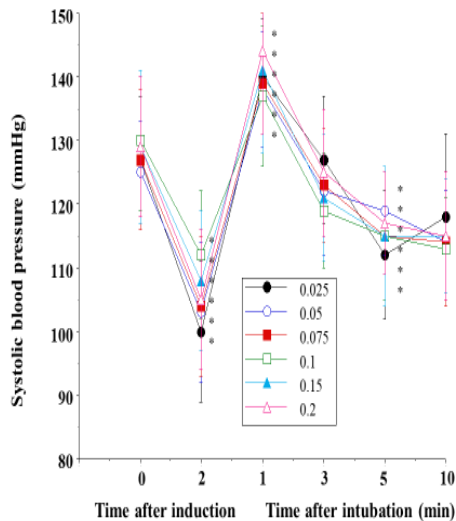


Fig.1

**Fig.1: Blood pressure.**

Systolic blood pressure was shown as mean  $\pm$  standard deviation.

\*:  $P < 0.05$  vs. the value at time 0

No significant differences were found among the groups.

Heart rate did not show any significant changes in all groups and no differences were observed among the groups (Fig. 2).

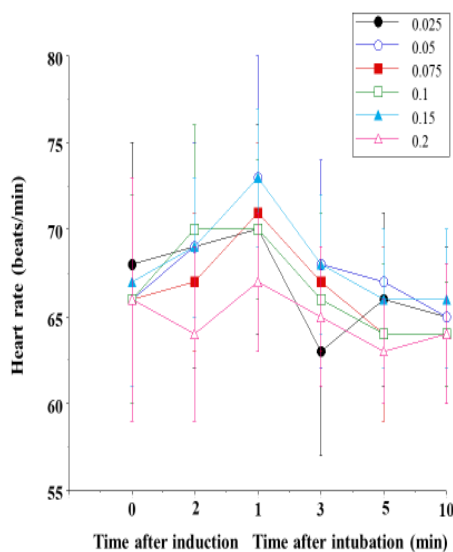


Fig.2

**Fig.2: Heart rate.**

Heart rate was shown as mean  $\pm$  standard deviation.

No significant differences were found among the groups.

BIS decreased as dose of midazolam increased after induction and 5 and 10 minutes after intubation (Fig. 3).

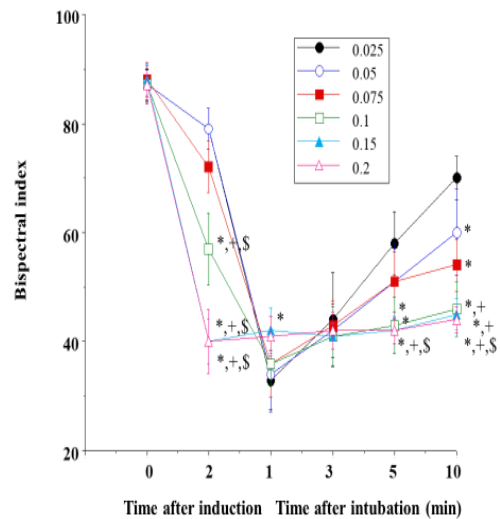


Fig.3

**Fig.3: Bispectral index**

Bispectral index was shown as mean  $\pm$  standard deviation.

\*:  $P < 0.05$  vs. group 0.025, +:  $P < 0.05$  vs. group 0.05,

\$:  $P < 0.05$  vs. group 0.075

The dose of propofol in patients judged as adequate induction decreased as the dose of midazolam increased (Fig. 4).

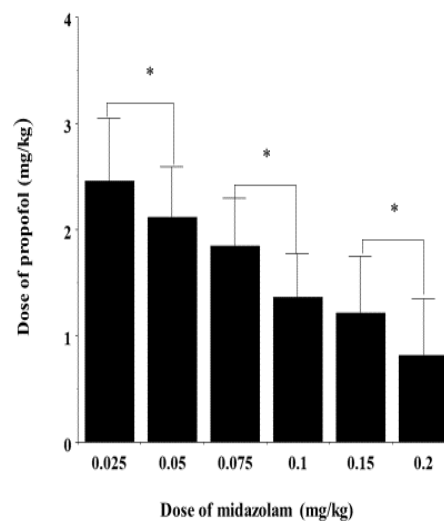


Fig.4

**Fig.4: Dose of Propofol and Midazolam.**

Propofol dose was shown as mean + standard deviation.

\*:  $P < 0.05$

The dose of propofol was  $2.46 \pm 0.59$ ,  $2.12 \pm 0.47$ ,  $1.85 \pm 0.45$ ,  $1.36 \pm 0.42$ ,  $1.22 \pm 0.53$ , or  $0.82 \pm 0.53$  mg/kg at midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.2 mg/kg, respectively.

**DISCUSSION**

We obtained the optimal doses of midazolam and propofol in co-induction of anesthesia using loss of verbal response, eyelash reflex, and blood pressure after

intubation as indicators. Midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.2 mg/kg and propofol  $2.46 \pm 0.59$ ,  $2.12 \pm 0.47$ ,  $1.85 \pm 0.45$ ,  $1.36 \pm 0.42$ ,  $1.22 \pm 0.53$ , or  $0.82 \pm 0.53$  mg/kg, respectively should be used after intramuscular midazolam 0.05 mg/kg 15 minutes before induction to have the changes in blood pressure in  $\pm 20\%$  of the control.

Usually opioids are used as well as propofol and/or midazolam for induction of anesthesia, but we did not use opioids in this study. Koh et al. reported that remifentanyl 0.25  $\mu\text{g}/\text{kg}/\text{min}$  decreased propofol dose for loss of consciousness from 1.74 mg/kg to 1.38 mg/kg and additional midazolam 0.05  $\mu\text{g}/\text{kg}$  decreased it to 0.92 mg/kg.<sup>[6]</sup> Therefore, opioids might have different effects on propofol alone and on combination of propofol and midazolam. To avoid these effects, we did not use opioids at induction in this study. This made the results of this study somehow different from common clinical practice. However, considered from changes in blood pressure in adequately anesthetized in the present study, propofol and midazolam might be enough to induce anesthesia. Of course, further studies including opioids for induction should be performed.

We administered midazolam 2 minutes before propofol administration. The peak effect of midazolam appears 2 to 5 minutes after bolus administration. Propofol has its peak effects at 1 to 2 minutes.<sup>[7]</sup> Therefore, midazolam should be administered first, and the optimal time to administer propofol should be 1 to 3 minutes after midazolam.<sup>[8]</sup> In addition, we used priming principle for vecuronium to facilitate faster intubation.

We administered intramuscular midazolam as a premedication 15 minutes before induction considering such situation. Premedication with intravenous midazolam 0.05 mg/kg 20 minutes before induction significantly decreased propofol dose requirement from 3.0 mg/kg to 2.4 mg/kg for loss of verbal contact, and from 7.6 mg/kg to 4.5 mg/kg for loss of response to pain in the study by Wilder-Smith et al.,<sup>[9]</sup> while Agrawal et al. reported that intravenous midazolam 0.05 mg/kg as a premedication 20 minutes before induction decreased induction dose of propofol from about 1.9 mg/kg to 1.3 mg/kg.<sup>[10]</sup> The great difference of propofol dose between the two groups might be due to fentanyl usage by Agrawal et al. We did not check the effects of premedication and we did not have the group without midazolam at induction. However, from the results of the study by Wilder-Smith et al.,<sup>[9]</sup> if only propofol was used for induction, about 4.5 mg/kg might be necessary after premedication with midazolam.

Pre-administration of midazolam 2 mg (about 0.025 mg/kg) decreased propofol induction dose from 2.38 mg/kg to 1.71 mg/kg in the study by Anderson et al.<sup>[11]</sup> Their patients were younger than ours, but they needed smaller dose of propofol in combination. They infused propofol at 66.7 mg/min but we did at 200 mg/min, and

they stopped infusion at loss of verbal response, but we used both verbal response and eyelash reflex. These differences might be the reason of the different propofol dose between the study by Anderson et al.<sup>[11]</sup> and ours. Cressey et al. reported that induction doses of the combination of midazolam and propofol were 0, 0.025, or 0.05 mg/kg and 2.7, 2.1, or 1.8 mg/kg in young, and 0, 0.025, or 0.05 mg/kg and 2.2, 1.4, or 1.1 mg/kg in aged patients, respectively.<sup>[12]</sup> Their doses were smaller than ours. They used fentanyl and they infused propofol at 66.7 mg/min. Midazolam 0.02 mg/kg decreased dose of propofol from about 1.2 mg/kg to 1.0 mg/kg for loss of verbal contact and from about 1.8 mg/kg to 1.7 mg/kg for insertion of airway.<sup>[5]</sup> Their doses were smaller than ours, because their patients were  $> 70$  years old and propofol was infused at 50 mg/min. The results of the study by Kataria et al. showed that midazolam 0.05 mg/kg 2 minutes prior to propofol decreased induction dose of propofol from about 1.3 mg/kg to 1.0 mg/kg.<sup>[13]</sup> Their patients were younger than ours, but they used BIS 45 as an indicator to stop propofol, and their systolic blood pressure after intubation was 20% over the control value that could be judged as not adequate in our study.

We did not study whether the interaction between midazolam and propofol was additive or synergistic. Both propofol and midazolam act on the  $\gamma$ -amino butyric acid (GABA)<sub>A</sub> receptor and additivity might be expected. However, they might affect different receptor sites.<sup>[14]</sup> Midazolam acts on the GABA<sub>A</sub> receptor complex via specific benzodiazepine receptors, while propofol directly activate GABA<sub>A</sub> receptor – chloride channel complex.<sup>[15]</sup> Midazolam and propofol interact synergistically to enhance currents evoked by low concentrations of GABA, but at higher concentration of GABA, the interaction was additive in the study using embryonic mouse neurons.<sup>[16]</sup> Midazolam potentiates GABA<sub>A</sub> receptor function primarily by increasing the binding affinity of the receptor for GABA, but propofol directly activates GABA<sub>A</sub> receptor in the absence of GABA and influences the kinetics of receptor desensitization.<sup>[16]</sup> The synergistic interaction between midazolam and propofol could result from midazolam-induced potentiation of the propofol-evoked current.<sup>[16]</sup>

Midazolam decreased required propofol dose for anesthesia, but the changes in blood pressure were the same for combination as for individual agents.<sup>[4]</sup> Co-induction of anesthesia with a combination of midazolam 0.3 mg/kg and propofol 0.8 mg/kg in old patients had less decrease of blood pressure before and after intubation than induction with propofol alone.<sup>[17]</sup> Midazolam decreases parasympathetic activity and does not change sympathetic activity.<sup>[18]</sup> Propofol increases parasympathetic activity and decreases sympathetic activity.<sup>[18]</sup> Therefore, combination might have stable hemodynamics.

**CONCLUSION**

After premedication with intramuscular midazolam 0.05 mg/kg, midazolam 0.025, 0.05, 0.075, 0.1, 0.15, or 0.2 mg/kg and propofol  $2.46 \pm 0.59$ ,  $2.12 \pm 0.47$ ,  $1.85 \pm 0.45$ ,  $1.36 \pm 0.42$ ,  $1.22 \pm 0.53$ , or  $0.82 \pm 0.53$  mg/kg, respectively were optimal dose combinations for induction of anesthesia to give stable hemodynamics.

**ACKNOWLEDGEMENTS**

Source of funding: no

Conflict of interest: no

**REFERENCES**

- Nishiyama T, Hirasaki A, Odaka Y, Ishii S, Ono T, Seto K. Induction of anesthesia with midazolam and thiamylal. *Jpn J Anesthesiol*, 1994; 43: 818-22.
- Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL. Response surface model for anesthetic drug interactions. *Anesthesiology*, 2000; 92: 1603-16.
- McClune S, McKay AC, Wright PMC, Patterson CC, Clarke RSJ. Synergistic interaction between midazolam and propofol. *Br J Anaesth*, 1992; 69: 240-5.
- Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth*, 1991; 67: 539-45.
- Jones NA, Elliott S, Knight J. A comparison between midazolam co-induction and propofol pre-dosing for the induction of anaesthesia in the elderly. *Anaesthesia*, 2002; 57: 649-53.
- Koh JC, Park J, Kim NY, You AH, Ko S H, Han DW. Effects of remifentanyl 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: 49(e9146). doi: 10.1097/MD.00000000000009164.
- Mould DR, DeFreo TM, Reece S. Simultaneous modelling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. *Clin Pharmacol Ther.*, 1995; 58: 35-43.
- Ong LB, Plummer JL, Waldow WC, Owen H. Timing of midazolam and propofol administration for co-induction of anaesthesia. *Anaesth Intensive Care.*, 2000; 28: 527-31.
- Wilder-Smith OH, Ravussin PA, Decosterd LA, Despland PA, Bissonnette B. Midazolam premedication reduces propofol dose requirements for multiple anesthetic endpoints. *Can J Anaesth*, 2001; 48: 439-45.
- Agrawal M, Asthana V, Sharma JP. Efficacy of intravenous midazolam versus clonidine as premedicants on bispectral index guided propofol induction of anesthesia in laparoscopic cholecystectomy: A randomized control trial. *Anesth Essays Res.*, 2014; 8: 302-306. doi: 10.4103/0259-1162.143117.
- Anderson L, Robb H. A comparison of midazolam co-induction with propofol pre-dosing for induction of anaesthesia. *Anaesthesia*, 1998; 53: 1117-29.
- Cressey DM, Claydon P, Bhaskaran NC, Reilly CS. Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. *Anaesthesia*, 2001; 56: 108-13.
- Kataria R, Singhal A, Prakash S, Singh I. A comparative study of efficacy of propofol auto-co-induction versus midazolam propofol co-induction using the priming principle. *Indian J Anaesth*, 2010; 54: 558-561. doi: 10.4103/0019-5049.72647.
- Orser BA, McAdam LC, Order S, MacDonald JF. General anaesthetics and their effects on GABA(A) receptor sensitization. *Toxicol Lett.*, 1998; 100-101: 217-24.
- Hara M, Kai Y, Ikemoto Y. Propofol activates GABAA receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. *Anesthesiology*, 1993; 79: 781-8.
- McAdam LC, MacDonald JF, Orser BA. Isobolographic analysis of the interactions between midazolam and propofol at GABA<sub>A</sub> receptors in embryonic mouse neurons. *Anesthesiology*, 1998; 89: 1444-54.
- Lim YS, Kang DH, Kim SH, Jang TH, Kim KH, Ryu SJ, Yu SB, Kim DS. The cardiovascular effects of midazolam co-induction to propofol for induction in aged patients. *Korean J Anesthesiol*, 2012; 62: 536-542. doi: 10.4097/kjae.2012.62.6.536.
- Win NN, Fukuyama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg*, 2005; 101: 97-102.