

THE CARDIOVASCULAR EFFECTS OF MIDAZOLAM CO-INDUCTION TO PROPOFOL FOR INDUCTION IN GERIATRIC PATIENTSKaushal Kabir¹, Sunil Arya²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: The aim of the study was to investigate whether a small dose of midazolam and lessening the propofol dosage could prevent the cardiovascular change at tracheal intubation for induction in geriatric patients. **METHODS:** ninety patients over 65 (ASA physical status 1, 2) scheduled for elective surgery received general anaesthesia with fentanyl and propofol or midazolam. Patients in group P (n= 45) were induced with 0.9% NaCl 0.03 ml /kg, propofol 1.2 mg/kg and fentanyl. Patients in group MP (n= 45) were induced with midazolam 0.03 mg/ kg, propofol 0.8 mg/kg and fentanyl. The time taken to reach loss of consciousness (LOC). After LOC 0.5 mg/kg of atracurium was given and tracheal intubation was performed. The mean blood pressure (MBP) and heart rate (HR) were recorded were induction as the base value, before intubation, immediately post intubation and 3 minutes after intubation. **RESULT:** compared with the base values, MBP at before intubation and # minutes after intubation was significantly decreased in group P and group MP (P <0.05). compared with group P, the decrease of MBP was significantly less at before intubation, immediately after intubation and 3 minutes after intubation in group MP (P<0.05). The time taken to reach LOC was significantly decreased in group MP compared with that in group P (P<0.05). There was no significant difference of HR at any time between the two groups. **CONCLUSION:** co-induction with midazolam and propofol could prevent a marked BP decrease at tracheal intubation for induction in geriatric patients.

KEYWORDS: aged, cardiovascular system, drug synergism, midazolam, propofol

INTRODUCTION: Aged patients require very careful attention and observation for induction of anaesthesia and endotracheal intubation because they are likely to have high frequency of side effects even with adult dose due to deterioration of organ function, change in autonomic nervous system and increase in drug sensitivity due to aging in comparison to young people.⁽¹⁾ In addition, in aged patients, special attention is required to avoid any serious decrease of heart rate (HR) because the risks of cardiac ischemia, cerebral ischemia, and cerebral infarction may increase even from temporary decreases of blood pressure (BP) and HR.

Propofol being used for induction of general anaesthesia has a rapid onset; it is therefore, a recommended intravenously infused anaesthetic agent for anaesthesia of the age. However, in aged patients, the sensitivity of propofol for the brain needs to be increased; therefore, anaesthetic effects are manifested as increased at the same dose.⁽²⁾

Also a problem arises when inducing the anaesthesia using propofol, whereby the prominent decrease of systolic pressure by 15- 40 % may be more prevalent in the aged. Therefore, in the aged patients, whose hemodynamic changes are severe, the use of co-induction method with an intravenously infused anaesthetic agent can escalate the efficacy and safety of the drug agent.^(4, 5)

ORIGINAL ARTICLE

Co-induction refers to a method in which anaesthetic agent is administered together with a small quantity of sedatives or another anaesthetic agent to reduce the dosage of the anaesthesia induction agent. This method is advantageous as it minimizes the side effects that can be manifested for induction of anaesthesia with the same or higher efficacy by using two or more drug agents as a combination compared to a single agent.⁽⁴⁾

It has been known that co administration of midazolam and propofol can reduce the inductive dosage of propofol by synergism of the narcotic effect,^(5,6) there has been no report in actual conditions on the cardiovascular changes occurring from the co administration of midazolam and propofol for induction of anaesthesia in geriatric patients. Therefore this study aimed to identify whether the induction of general anaesthesia performed by the co administration of propofol and fentanyl in geriatric patients can reduce the dose of propofol and whether co administration with a small amount of midazolam cannot only reduce the cardiovascular changes being manifested before and after the endotracheal intubation.

MATERIALS AND METHODS: This study was initiated after obtaining hospital ethics committee approval and written informed consent from all the patients on the day before the surgery after explaining to them the objectives and methods of this study. This study was performed in 90 American society of Anesthesiologists (ASA) physical status patients' grade I-II whose ages were over 65 years and who were scheduled for elective surgery under general anaesthesia.

Any patient with a history of hypertension or diabetes mellitus, or currently under treatment for respiratory diseases, patients with history of myocardial infarction or cerebral infarction, patients with dementia or psychiatric patients, patients under dialysis treatment due to renal failure or patients in whom it is difficult to perform endotracheal intubation at over Mallampati class 3 are all excluded from participation in this study.

The patients fasted for over 8 hours before surgery and no premedication was given. After a patient was admitted to the operation room, an electrocardiogram (ECG), non-invasive manometer, and a pulse oximeter were attached to the patient. After the patient was stabilized, the mean BP and HR as well as pulse saturation were measured as a baseline. As premedication, 0.2 mg of glycopyrrolate was infused by intravenous administration and for pre-oxygenation before induction of anaesthesia; all patients were asked to breathe deeply 10L/min oxygen 8 times for one minute.⁽⁷⁾

Although deep breathing of 100% oxygen 4 times, for 30 seconds is the proper procedure for young and healthy patients, in the aged patient in whom the desaturation is rapid, the time for desaturation needed to be extended in order to maximize oxygenation, not only of the pulmonary alveolus and arteries but also the tissues and veins. In this study in order to maximize oxygenation in the shortest amount of time, when applying the aforementioned procedure, during the operation, the oxygen saturation was maintained at over 99% in all patients.

Anaesthesia was initiated with 2 µg/kg/hr fentanyl using a drug infusion pump. The subjects were randomly assigned into two groups, one group with co administration of midazolam and propofol and other with administration of propofol alone as the single agent. The groups were set as the test group (MP group n= 45) and the control group (P group; n = 45). In the group MP test group, midazolam 0.03 mg/kg was intravenously infused simultaneously with the initiation of fentanyl administration and propofol was added as 0.8 mg/kg after 2 minutes, whereas in the control group – P, 0.9% NaCl 0.03mg/kg was infused simultaneously with the initiation of fentanyl administration in addition to the administration of propofol at 1.2mg/kg 2 minutes later.

ORIGINAL ARTICLE

The unconsciousness was confirmed by the non-reaction of patients to the verbal order “please open your eyes” together with loss of lid reflex. A muscle relaxant, atracurium 0.5 mg/kg, was intravenously injected 60 seconds after the administration of propofol and bag and-valve ventilation was performed for 3 minutes.

After confirmation of sufficient muscle relaxation, the endotracheal intubation was carried out. 5 minutes after the initial administration of fentanyl endotracheal intubation was performed, fentanyl was administered with a reduced dose of 0.5µg/kg/hr and the anesthesia was maintained with sevoflurane 1.5% oxygen at 1.5L/min and air at 2.5L/min. also mechanical ventilation was carried out in order to maintain P_{ETCO_2} at 30-35mmhg.

Mean blood pressure (MBP) and HR were measured and recorded at the baseline before the induction of anaesthesia (B), immediately before performing endotracheal intubation (BI) immediately after performing endotracheal intubation (PI0) and at 3 minutes after endotracheal intubation (PI3). It was decided that when the patients HR has decreased below 45 times per minute, atropine 0.5 mg was to be intravenously injected, whereas when the systolic BP of the patient after performing endotracheal intubation was lower 80mmhg, ephedrine was to be given through intravenous administration with an increase of dose by 5mg.

For statistical analysis, the study used SPSS (version 13.0) and all results were indicated as mean \pm standard deviation. Inter group comparison by time points was conducted using an unpaired T-test and the intra group variations of MBP and HR according to time were analyzed by using repeated ANOVA measures. If the P value was less than 0.05, it was determined as statistically significant.

RESULTS: There was no intergroup significant difference in age, gender, height, body weight, BMI and in the ASA physical status grading classification (table 1).also there was no inter-group significant difference observed of BP and HR at the baseline. For the time taken until loss of consciousness after intravenous administration of propofol, the MP group (38 \pm 10.8) showed a significantly shorter time compared to the group P (53 \pm 12.1). For the mean BP, the MP group showed significant small decreases of BP at BI, PI0 and PI3, compared to the P group.

The MP group showed significant decreases of BP at BI (29.7%) and at PI3 (23.2%) compared to those at the baseline (figure 1). The HR group showed lower values overall in the MP group than in the P group from inter group comparison but had no statistically significant difference. Also, from both the groups MP and P, there was no significant difference in the HR by each time point. (Figure 2) Although bradycardia requiring the use of atropine had not occurred in both the groups, # patients of the group administered with 1.2 mg/kg propofol had shown a decrease of systolic BP; they were thereby excluded from the study subjects after intravenous administration of ephedrine 5 mg.

	Group MP (n=45)	Group P (n=45)
Gender (M/F)	20/25	23/22
Age(yrs)	70 \pm 4.2	68.3 \pm 3.3
Height (cm)	163.5 \pm 9.4	162.4 \pm 7.8
Weight(kg)	62.6 \pm 9.1	60.8 \pm 8.9
BMI (kg/m ²)	23.4 \pm 2.3	23.0 \pm 2.4

TABLE 1: DEMOGRAPHIC AND OTHER DATA (MEAN \pm SD)

ORIGINAL ARTICLE

Values are mean \pm SD or number of patients. Group MP; co-induction with midazolam 0.03 mg/kg and propofol 0.8mg/kg. Group P; induction with propofol 1.2 mg/kg only. BMI; body mass index.

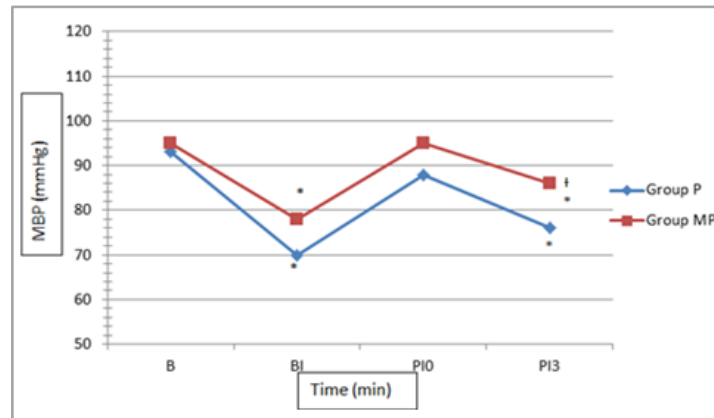


Fig. 1: changes of mean blood pressure (MBP) during induction of anaesthesia

Values are mean \pm SD. Group MP; midazolam + propofol, Group P Propofol alone. B: Baseline BI before induction P10: just post intubation, P13 3 minutes after intubation. *P<0.05, compared with baseline in each group †P<0.05, compared with group P

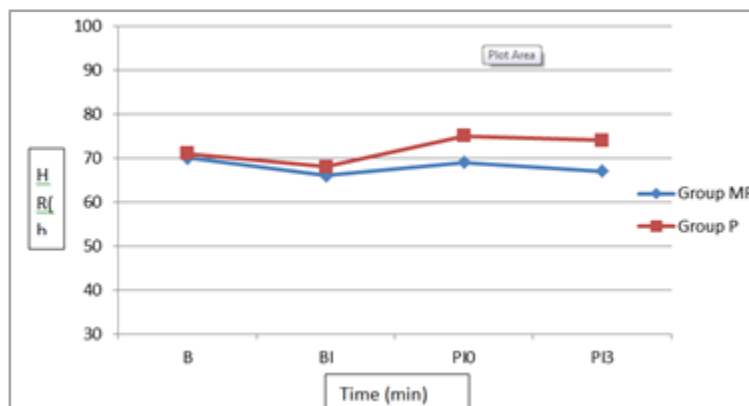


Fig. 2: changes of heart rate (HR) during induction of anaesthesia

Values are mean \pm SD. Group MP; midazolam + propofol, Group P Propofol alone. B: Baseline BI before induction P10: just post intubation, P13 3 minutes after intubation

DISCUSSION: In the results of this study, it was identified that the group with co induction of general anaesthesia with combination of midazolam and propofol in aged patients did not have large scaled decrease of MBP at the point of immediately before performing endotracheal intubations well as the time points of 1 minute and 3 minutes after performing endotracheal intubation, in comparison to the group with the single induction of propofol only (P<0.05).

ORIGINAL ARTICLE

Even compared to the BP at the baseline, the group with co induction did not show any increase of mean BP at the time point of 1 minute after performing endotracheal intubation. To this end, it is considered that using midazolam as a co-induction drug in combination with propofol for induction of anaesthesia in aged patients, can prevent sudden BP decreases occurring immediately before and at the time point of 3 minutes after, performing endotracheal intubation as well as notable BP decreases incurring between immediately after the endotracheal intubation and at 3 minutes after endotracheal intubation with midazolam.

During the operation, sympathetic tone increase in the patients, causing cardiovascular change,⁽⁸⁾ and in particular, the variation is presented in larger scale in aged patients. Patteniti et al,⁽⁹⁾ in their study on the physiologic characteristics of aged patients, found that physical organic dysfunction and incurrance of additional diseases had increased in proportion to the age, and that in their central nervous system functions, cardiovascular functions, hepatic functions, renal functions and pulmonary functions were reduced, resulting in a high ratio of pre and post-operative morbidity and mortality.

Ryu⁽¹⁾ also suggested that in aged patients, organic functions were decreased while cardiovascular functions were increased in addition to new incurrances of disease affecting pharmacodynamics and pharmacokinetics including diabetes mellitus and abnormality in renal function along with the aging symptoms; therefore, even if the same dose of drug effects would be presented as increased due to the high drug sensitivity, in addition to the highly likely frequency of side effects.

Moreover, the non-compliant heart of the aged patients also led to large scale variation in ventricular preload and cardiac output as responses to even small variations of venous return. Therefore, Ryu had suggested that the aged patients do not have a good level of compensation to the decrease of blood volume due to notable reductions in diastolic myocardial functions, the control of the HR by a baroreceptor, adrenergic receptor responsiveness and vascular compliance. Propofol as alkylphenol group drug agent presents direct myocardial depression effect due to the negative inotropic effect⁽⁶⁾ and the cardiovascular inhibition effects through the reduction of systemic vascular resistance by vasodilative action.⁽¹⁰⁾

The administration of a suitable dose for the induction of anesthesia inhibits the baroreflex mechanism, inhibiting the acceleration of HR due to decrease of arterial pressure. These results maybe worsened even further by factors such as a large dosage, infusion at rapid speeds, and old ages. Moreover, in aged patients, the blood concentration of propofol could be maintained at a high level as the patients had quite a low clearance rate of propofol and small central compartment capacity,⁽¹¹⁾ the conditions allow the cardiovascular inhibition effects to be expressed more prominently in aged patients.

Therefore, when performing the induction of anaesthesia using propofol on aged patients or on patients whose cardiovascular system is unstable, a careful readiness for the procedure is required with a pre-emptive expectation of a high prevalence of serious BP decreases in proportion with IV doses and speeds among aged patients in comparison to young patients.^(3,12) In this study, it took 5 minutes from the induction with propofol until the BP measurement after the endotracheal intubation and it was considered that the BP had not reached the lowest BP incurring at the post propofol administration due to stimulation by the endotracheal intubation.⁽¹⁾

ORIGINAL ARTICLE

It is expected that a serious BP decrease might have incurred if measured at 5 minutes after the endotracheal intubation under the condition of no stimulation. However, it was determined that a serious BP decrease or a prolonged time of such decrease was likely to have harmful effects on the aged patient, and that there was a realistic limitation in idly waiting for 5 minutes under the conditions until processing the invasive procedure or surgery after the endotracheal intubation.

Moreover, because the results presented a significant inter group difference in BP variation trends for 3 minutes after the endotracheal intubation, BP was measured only up to 3 minutes after the endotracheal intubation. Charlson et al⁽¹³⁾ had reported that the decrease of intra-operative BP (decrease of more than 30% from the arterial pressure before induction of anaesthesia) had caused rein fraction in 20 % of patients who had myocardial infarction; in addition the post-operative complication of ischemic heart disease was shown with a high prevalence when the mean myocardial decrease of more than 20 mmHg had been sustained for 5 to 59 minutes.

Therefore, when performing induction of anaesthesia in aged patients, measures should be taken to prepare for the possible incidence of a serious BP decrease within 5 minutes after endotracheal intubation, and if such a decrease is incurred, that the time for sustenance of low blood pressure status should be shortened by using a position change or inotropics.

From a preliminary study conducted prior to this study in aged patients over 65 years old, a few patients did not reach unconsciousness when administered propofol 1.0 mg/kg, and a few patients showed decrease of systolic pressure below 70mmHg when administered 1.4 mg/kg. Given these results, in this study, the administration dose of propofol for the group with propofol only was set at 1.2mg/kg. Schüttler and Ihmsen⁽¹⁴⁾ recommended using propofol by reducing its dose for adults by over 40% because the clearance rates of propofol could be reduced in aged patients over 60 years old.

On the other hand, Olmos et. Al.⁽¹⁵⁾ reported that the required dose of propofol was reduced by 37 % in the patients in over 60 years old group who had not received premedication for induction of anaesthesia by controlled induction of target concentration in comparisons to the under 40 years old patients. They also reported that as the age increased by 10 years, the required dose was to be reduced accordingly.

In addition, as aged patients are sensitive due to reduction of total body clearance rate according to the pharmacokinetic variation, it is important to increase or decrease the dose of medication depending on the age. Generally, it is recommended that the medication which can maintain the cardio-pulmonary functions safely when the patient is over 40 years old should be administered by reducing the medication dose by 10 % to 12 % at each 10 year increase and that medication should be used that presents a short action time and a fast recovery.⁽¹⁸⁻²¹⁾

In this study, the dose of 1.2 mg/kg propofol for the group with propofol only was administered by reduction of adult dose by 20-52% which was considered as 1.5-2.5 mg/kg. Midazolam is water soluble benzodiazepine with a fast onset of action of 2 to 3 minutes and a short distribution half-life of 5 to 10 minutes. It has been widely used recently as the premedication agent of anaesthesia because it was effective in resolving the anxiety of surgery and stabilizing the cardiovascular system during the perioperative period.^(20, 21)

When performing the co induction of anaesthesia by combining midazolam and propofol, the single intravenous bolus administration had shown the synergistic action of sleep effectiveness, indicating that such co-induction presents the effect of approximately 25-35% higher dose reduction

ORIGINAL ARTICLE

in comparison to single respective doses of each medication.⁽²²⁾ Kim et. Al.⁽⁸⁾ reported that a prior administration of 2 mg (0.032 mg/kg) midazolam combined with sustained intravenous infusion of propofol reduced the sleep inducing dose of propofol by 29%. To this end, in this study, instead of setting the administration dose of midazolam as 0.03 mg/kg in the MP group, the administration dose of propofol had been reduced to 0.8mg/kg.

Unlike this study, where the single intravenous bolus administration has been used, Teh et al⁽²³⁾ reported that the cause of sleep effect synergistic action of midazolam and propofol was pharmacodynamics interaction between the two drug agents at the GABAA of the brain but no synergistic action of the cardiovascular system. The objective of this study was to identify not only the synergistic action on the sleep effect but also the hemodynamic synergistic action against the inhibition of cardiovascular system.

The result showed that the co-induction of anaesthesia in aged patients by a combination of midazolam and propofol had synergistic action in terms of sleep-inducing effect as well as hemodynamic effects. In this study, fentanyl was administered at a certain rate of 2µg/kg/hr from the beginning of anaesthesia induction until the performing of endotracheal intubation and it was administered at a reduced amount of 0.5µ g/kg/hr after 5 minutes.

Yim et al⁽²⁴⁾ also reported that the continuous intravenous administration in the use of target effect site concentration for the induction of anaesthesia with the co-administration of remifentanyl and propofol in aged patients has more hemodynamic stability than a fast single intravenous bolus administration, less incidence of severe low blood pressure before performing the endotracheal intubation.

Chung and lee⁽²⁵⁾ reported that if propofol is infused slowly at 20 mg/kg/hr for the induction of anaesthesia with a single use of propofol only in aged patients, the dose of 2.0 mg/kg does not cause a significant decrease of BP in comparison to the dose of 1.5 mg/kg. In this study, even when the above drug agent was used by the single intravenous administration, there was no case in which severe low blood pressure with systolic pressure below 70 mmHg was presented.

In conclusion, when performing the induction of anaesthesia in geriatric patients over 65 years using the combination of propofol and fentanyl, the co-induction with reduced dose of propofol to 0.8mg/kg in combination with midazolam 0.3 mg/kg can prevent the incidence of prominent of blood pressure incurring before and after the endotracheal intubation.

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ORIGINAL ARTICLE

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ORIGINAL ARTICLE

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