

Effect of Midazolam Pre-medication on Induction Dose of Propofol in Adult Patients in Elective Surgery

Aher Pranjali Y¹, Sangale Swapnil V², Subhedhar Rajesh³, Murugraj Shivkumar⁴, Selvarajan N⁵

^{1,2}Assistant Professor, ³Professor and Head, Department of Anaesthesia, Shri Bhausaheb Hire Govt Medical College, Dhule, Maharashtra 424001, India. ⁴Consultant Anesthetic, ⁵Professor and Head, Department of Anaesthesia, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu 641014, India.

Abstract

Introduction: The study based on that midazolam pre-medication reduces the induction dose and cost of propofol. **Aims:** To study effect of midazolam pre-medication on induction dose of propofol in adult patients. **Methods:** A prospective randomized, double blind control study was conducted. Total 60 patients (16–45 years) were divided into 2 groups. Group 1 received 0.05 mg/kg of Midazolam and Group 2 received Normal Saline. We compared the induction dose of propofol in both groups, taking loss of verbal contact as the end point. Additionally, changes in hemodynamic status like blood pressure and heart rate and induction time were studied and compared in both groups. **Results:** The dose of Propofol required to induce anesthesia in Midazolam group was 1.32 mg/kg and 2.27 mg/kg in the control group. The hemodynamic changes in Midazolam group compared to NS were non-significant. **Conclusion:** We recommend midazolam when used in combination with propofol reduces the dose of propofol and the time required for induction.

Keyword: Pre-medication; Midazolam; Induction; Propofol.

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Introduction

Pre-medication¹ refers to administration of drugs before induction and maintenance of anesthesia. It allays pre-operative fear, anxiety and tension. It facilitates rapid and smooth induction of anesthesia. It produces amnesia, sedation and analgesia. It also potentiates the anesthetic effects and hence may decrease the anesthetic requirement. Srivastava U *et al.*, and Amrein R *et al.* mentioned in their²⁻⁴ that "Co-induction" is concurrent administration of two or more drugs that facilitate induction of

anesthesia. McKay AC *et al.* documented synergism in the study.^{5,6}

Propofol is well-established as anesthetic inducing agent than thiopentone. Propofol and midazolam combination is commonly used for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression.⁷⁻⁹

Some recent studies have shown that administration of midazolam pre-medication reduces the intravenous induction dose of propofol. It reduces pain due to IV propofol and hence it reduces cost of the anesthesia.^{10,11}

Corresponding Author: Aher Pranjali Y, Assistant Professor, Department of Anaesthesia, Shri Bhausaheb Hire Govt Medical College, Dhule - 424001, Maharashtra, India.

E-mail: aherpranjali@gmail.com

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Midazolam and propofol co-induction also lead to minimal hemodynamic changes. The technique of co-induction using two or more agents to induce anesthesia has been studied and synergism is reported between number of induction agents and midazolam.^{7,9,12}

Objectives

To study the effects of midazolam pre-treatment on induction dose of propofol anesthesia in adult patients and also to study the hemodynamic changes with and without midazolam to propofol.

Materials and Methods

A randomized control double blind study was conducted at the Department of Anesthesia at our institute during the period of July 2010–July 2012, after obtaining the approval of the institutional ethical committee. After obtaining written informed consent, total 60 patients belonging to both sex who were undergoing elective surgical procedures under general anesthesia, were enrolled.

Inclusion Criteria

ASA Grade 1 and 2 of aged between 15 and 45 years who were scheduled for various elective surgical procedures under GA.

Exclusion Criteria

Difficult intubation, patients having pharyngeal pathology, cardiovascular and pulmonary disease, on medications like benzodiazepine, clonidine or beta blockers.

Pre-anesthetic evaluation was done in all patients a day prior to surgery. After detailed systemic evaluation, Patients who do not fall into our inclusion criteria were excluded. All patients were explained and after reassurance, informed consent was taken. All patients were kept nil by mouth for at least 6 hours prior to surgery. No pre-medication was given. Routine investigations like hemoglobin and urine examination were done in all patients. Blood sugar, Serum Creatinine and ECG were done in patients with age more than 40 years. On arrival in the operation theatre, IV access was done with 18 G canula. ECG, pulse oximeter and NIBP were applied for monitoring. Patients were then assigned randomly into two groups namely: Group 1 (Midazolam + Propofol) and Group 2 (Saline + Propofol), according to the sealed envelope

method by the anesthetic team not participating in the study but the researcher and the patient were unaware of their group. Either of the study drugs as priming were administered IV (Group 1- 0.05 mg/kg of Midazolam, Group 2- normal saline) according to the randomization by the team, after pre-oxygenation for 3 minutes, the study drugs was given IV diluted in 10 ml of normal saline over a period of 10 seconds. After 90 seconds, anesthesia was induced by inj propofol 10 mg/ml in a 20 ml syringe at rate of 1 ml/second, keeping continuous verbal contact with the patient till loss of verbal contact and the total amount of propofol given was noted. Following this regular anesthesia was given with oxygen, nitrous oxide and inhalational anesthetic agent with or without muscle relaxant as per the needs of the procedure. Parameters assessed were induction time, dose of propofol, hypotension (Occurrence of blood pressure < 90 mmHg systolic), bradycardia (Incidence of pulse rate < 60 min) and pain on injection of propofol. Statistical Analysis was done with SPSS and data was expressed as mean (standard deviation) for continuous variables and proportion for qualitative variables. Student's *t*-test was used to test the statistical significance for quantitative variables and chi-square or fisher exact test for qualitative variables. $p < 0.05$ was considered statistically significant.

Results

The average age of the total patients were 35.45 years ranging from 15 to 45 years. In the group 1, the mean age was 35.9 years, in group 2 it was 35 years. Out of the 60 cases, 31 were males and 29 females. There were 11 male and 19 female patients in group 1, 20 male and 10 female patients in group 2. The mean weight of patients was 60.2 kg ranging from 40 to 85 kg. In the group 1, the mean weight was 60.73 kg, in group 2 it was 59.20 kg. The majority of the patients in all the groups were ASA Gr 1 (90%) however, 6 (10%) were in ASA Gr 2 of both groups. The average requirement of Propofol varied significantly between the groups ($p < 0.001$), with mean 80.33 mg in Group 1 and 134.66 mg in Group 2 Mean Time required for induction in Group 1 was 31.5 seconds and in Group 2 was 54.5 seconds ($p < 0.001$). Hypotension noted after induction was 26.7% in Group 1 (midazolam + propofol) and 13.3% in Group 2 (NS + propofol) while 10% in Group 2 of patients only had bradycardia. Both findings were non-significant. Pain at the time of induction was 3.3% of patients in Group 1 and 36.7% in Group 2. So 96.7% in Group 1 and 63.3%

in Group 2 patients didn't have complaint of pain (χ^2 -10.41 and $p < 0.01$) showed in (Tables 1-5).

Table 1: Gender distribution of the patients

Sex	Group 1 (%)	Group 2 (%)
Male	11 (36.6%)	20 (66.7%)
Female	19 (63.7%)	10 (33.3%)
Total	30 (100%)	30 (100%)

Table 2: Age and weight of the patient

Parameter	Group	Mean	SD*	t-Value	Probability
Age	1	35.90	7.685	0.463	0.645
	2	35	7.353		
Weight	1	60.73	11.307	0.628	0.532
	2	59.20	7.122		

*SD: Standard deviation.

Table 3: Induction dose of propofol

Group (n)	Mean Dose	SD*	p - Value
Group 1 (30)	80.33	28.61	< 0.001
Group 2 (30)	134.66	24.03	

*SD - Standard deviation.

Table 4: Induction time of propofol

Group (n)	Mean	SD*	p - Value
Group 1 (30)	31.5	12.26	p - Value < 0.001
Group 2 (30)	54.5	14.70	t -Value 6.581

*SD - Standard deviation

Table 5: Hemodynamic changes

Parameter		Group 1 (%)	Group 2 (%)
Hypotension	Present	8 (26.7%)	4 (13.3%)
	Absent	22 (73.3%)	26 (86.7%)
Bradycardia	Present	0 (0%)	3 (10%)
	Absent	30 (100%)	27 (90%)
Pain	Present	1 (3.3%)	11 (33.3%)
	Absent	29 (96.7%)	19 (66.7%)
Sedation	Present	1 (3.3%)	0 (0%)
	Absent	29 (96.7%)	30 (100%)

Discussion

Propofol is a popular intravenous agent used to induce for general anesthesia, with a property to suppresses the upper airway reflexes adequately apart from producing a rapid induction. When used as a sole agent, children require a larger dose of propofol for insertion of laryngeal mask airway than adult.^{7,13} This large dose needed for induction may be associated with hemodynamical and respiratory effect like hypotension, bradycardia, apnea or

hypoventilation. It is currently considered 'gold standard'^{14,15} for laryngeal mask insertion. Pre-dosing with Midazolam is a reliable and effective method of reducing Propofol requirement. This study was undertaken to see the effectiveness of midazolam pre-medication on induction dose of propofol in adult patients. In our study, induction dose, induction time, hypotension, bradycardia and pain were compared between both groups. In our study, mean induction dose was 80.33 mg in Group 1 while 134.66 mg in Group 2 ($p < 0.001$) when loss of response to verbal command, loss of eye lash reflex and loss of consciousness was taken as end point of induction.¹⁰ Same observed in Shahin Jamil *et al.* study¹⁶, that midazolam pre-medication is effective in reducing the induction dose of propofol and also the adverse effects due to higher induction dose of propofol. It also decreased the incidence of apnoea, but no clear benefits in terms of ease of LMA insertion and cardiovascular stability. Shahin Jamil *et al.* conducted a study on 60 ASA 1 and 2 patients, aged 15-45 years for various surgical procedures with 30 patients in each group ($n = 30$). Group A (study group) received 0.05 mg/kg midazolam while Group B (control) had saline as a pre-medication intravenously, followed by Fentanyl 1 mg/kg after 90 seconds of pre-medication. All patients were induced with propofol (1.5 mg/kg) 90 seconds after fentanyl bolus. Our study can be compared with another study conducted by Kumar A *et al.*¹⁷ who observed that there was 27.48% reduction in the induction dose of Propofol by applying priming principle. In his study¹⁷ both the control group and the Propofol priming group received Midazolam (0.05 mg/kg) as a pre-medication and Fentanyl 15 minutes prior to the induction. In study of Oliver H G Wilder-Smith¹⁸ which was a controlled, randomized, double blind prospective study of 24 patients, who received either midazolam 0.05 mg/kg or saline placebo as IV pre-medication 20 minutes prior to induction, concluded midazolam pre-medication reduces the induction dose of propofol without affecting hemodynamics. Anderson L *et al.*, Short TG *et al.*, McClune S *et al.*, used midazolam and propofol combination for inducing patients and concluded in their study that midazolam and propofol shows synergistic interactions when midazolam used in sub-anesthetic doses and reduces the dose of propofol required for induction via a synergistic action.^{4,5,6,7,9} In various studies like Driver IK *et al.*¹⁹, Jones Na *et al.*²⁰, Gill PS *et al.*²¹, Cressey DM²², Martlew RA *et al.*²³ observed that use of midazolam reduces the induction dose of propofol and also acts synergistically.

We also found significant induction time of propofol. Mean induction time of Group 1 was

31.5 seconds and that of Group 2 was 54.5 seconds. Our findings are comparable with study of Yushi U Adachi, Kazuhiko Watanable *et al.*²⁴, McKay AC.⁵

Bradycardia noticed only in 3 patients (10%) of Group 2 and none in Group 1 which was not significant. Our findings agrees with Goel S *et al.*²⁵, Djaiani G *et al.*²⁶ and Whitwan *et al.*²⁷, who used midazolam as co-induction agent along with propofol, noticed bradycardia which was non-significant. Though hypotension observed at the time of induction was higher in Group 1 (26.7%) than in Group 2 (13.3%) but it was not significant. This observation can be compared with observations of Djaiani G *et al.*²⁶, Anderson *et al.*⁴, Jones Na *et al.*²⁰, Short TG *et al.*⁷, Reinhart DJ *et al.*²⁸ found no significant difference in hypotension observed in their studies when midazolam and propofol are used as co-induction agent.

Pain observed at the time of induction was 3.3% in Group 1 and 36.7% in Group 2 which was a significant ($p < 0.01$). Less pain was observed in patients who received midazolam before propofol, in study of Gill PS *et al.*²¹, Edomwonyi N *et al.*¹¹, Leena Jalota *et al.*¹⁰

Conclusion

This study shows that Midazolam if used as a co-inductant, significantly reduces the induction dose and induction time of Propofol anesthesia. It also reduces the pain caused by intravenous propofol. It did not produce significant hemodynamic instability or any undue delay in recovery. So we can recommend midazolam as a co-inducing agent and it also reduces the cost of propofol required for induction which is beneficial for our patients in a developing country.

Key Message

Midazolam pre-medication reduces the induction dose and time for propofol.

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Competing Interest: None stated.

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