Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - I): 1541-1545
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.8

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

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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.

How to cite this article:

Aher Pranjali Y, Sangale Swapnil V, Subhedhar Rajesh *et al.* Effect of Midazolam Pre-medication on Induction Dose of Propofol in Adult Patients in Elective Surgery. Indian J Anesth Analg. 2019;6(5 Part-1):1541-1545.

Introduction

Pre-medication[1] refers to administration of drugs before induction and maintenance of anesthesia. It allays pre-operative fear, anxiety and tension. It facilitate 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 their[2–4] 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 profopol and hence it reduces cost of the anesthesia.[10,11]

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Received on 15.05.2019, **Accepted on** 08.06.2019

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.

Meterials 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 atleast *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 continous 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 (Occurence 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 continous 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 gruop. 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*	
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: Hemodynemic 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. Predosing 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, hypotesion, 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.* study[16], 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-medicantion 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 study[17] 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-Smith[18] 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 DM[22], 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 ued 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 signifant hemodynamic instability or any undue delay in recovery. So we can recommend midazolam as a co-inducting agent and it also reduces the cost of propofol required for induction which is beneficial for our patients in a developing country.

Key Massage

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

Source of support: None.

Conflicting interest: None stated.

Competing Interest: None stated.

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