European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 08, Issue 04 , 2021

# Effect Of Midazolam Premedication On Dose Of Propofol When Given As Infusion For Induction Of Anaesthesia: A Randomized Controlled Trial

**Dr. Dewendra J. Gajbhiye**

Classified Specialist (Anaesthesiology), Command Hospital (NC), Udhampur, Jammu & Kashmir, India.

## Abstract

**Background:** Propofol is a popular anaesthetic agent used for induction of general anaesthesia. However, it causes cardio-respiratory depression in vulnerable patients.

**Materials and Methods:** This prospective, randomized and controlled trial was conducted on 60 patients admitted for elective neurosurgical procedure after ethical clearance from Institutional Ethics Committee. After written informed consent, the patients were randomly allocated to two groups, I and II of 30 each. Group I received Inj. midazolam 0.02 mg/kg as premedication five minutes before induction with propofol infusion. Group II received only propofol infusion for induction of general anaesthesia. Total dose of propofol required for induction of anaesthesia was noted. Haemodynamic parameters were noted from baseline till 08 minutes post laryngoscopy and intubation.

**Results:** Samples in both the groups were comparable with respect to age, weight and gender. On comparison with the standard bolus dose of propofol (2mg/kg) for induction, reduction in the doses of propofol in Group I and Group II were 0.7 mg/kg and 0.3 mg/kg respectively. The reduction in the dose of propofol in Group I as compared to Group II was 0.4 mg/kg i.e. 20%. This difference was statistically significant ($P<0.001$). No statistically significant difference in the haemodynamic parameters between the two groups was observed ($p>0.05$).

**Conclusion:** Propofol infusion after midazolam premedication reduces the dose of propofol for induction of general anaesthesia and confers haemodynamic stability

**Keyword:** Propofol, midazolam, induction, infusion, premedication

## Introduction

Induction of general anaesthesia by intravenous route is the most commonly practiced technique due to introduction of newer and safer anaesthetic agents. However, search of an ideal intravenous anaesthetic agent for induction of general anaesthesia is still ongoing. An ideal anaesthetic agent used for induction of general anaesthesia must have rapid onset and

offset of action. It must confer haemodynamic stability. It should not get accumulated and have active metabolites. It must have analgesic and amnesic properties. It should be compatible with all solutions and should have longer shelf life. It should be painless on injection [1, 2].

Modern intravenous anaesthetic agents like propofol and midazolam possess most of the characteristics of an ideal induction agent [3]. But they have certain undesirable side effects offsetting the smooth course of anaesthesia. Propofol has drawback of causing cardio-respiratory depression in geriatric and dehydrated patients & in patients with cardiovascular compromise [4].Some investigators used different drug combinations with propofol for induction of general anaesthesia which decreased side effects mainly by reducing dose of individual drugs by synergism [4, 5]. Midazolam is demonstrated to be hypnotically synergistic with propofol as a premedicant or coinductant for general anaesthesia [6]. It was observed by many workers that target controlled infusion of propofol for induction of anaesthesia was safer than bolus dose given at random rate [7]. This study compared induction with propofol infusion after midazolam premedication versus propofol infusion only and the effects on hemodynamic parameters.

## Materials and Methods

This prospective, randomised and controlled trial was carried out at a tertiary care teaching hospital spanning over 12 months. Ethical clearance for the study was obtained from Institutional Ethics Committee. After written informed consent, 60 patients of either sex were randomly allocated to two groups of 30 each- Group I and Group II receiving Inj. midazolam 0.02 mg/kg as premedication five minutes prior to induction with propofol infusion and only propofol infusion respectively for induction of general anaesthesia.

### Inclusion Criteria

- Age between 18 to 65 years.
- Patients undergoing elective neurosurgery under general anaesthesia.
- ASA (American Society of Anaesthesiologists) physical status grade I & II patients.

### Exclusion Criteria

- Emergency surgery.
- Patients with sinus bradycardia, heart block and bronchospastic airway diseases.

Baseline Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean arterial pressure (MAP) were noted.

### Premedication

Patients in both the groups were premedicated with Inj. glycopyrrolate 0.004 mg/kg and Inj. fentanyl 0.002 mg/kg intravenously half an hour before induction of general anaesthesia. Patients in Group I received Inj. midazolam 0.02 mg/kg intravenously 05 minutes prior to induction of anaesthesia.HR, SBP, DBP & MAP were recorded before premedication with glycopyrrolate and fentanyl (preoperative baseline), at 15th and 25th minute after premedication with glycopyrrolate & fentanyl in both the groups and at 30th minute (preinduction) in ‘Group I’ to observe the effect of midazolam premedication.

### Induction

All the patients were preoxygenated with 100% oxygen for 05 minutes. Patients in both groups were induced with Inj. propofol infusion using syringe infusion pump at the rate of 200ml/hr i.e.33.3 mg/min. ‘Loss of verbal contact’ was taken as the end point of induction and propofol infusion was stopped. The dose of propofol infused was recorded.

Endotracheal intubation was facilitated with Inj. rocuronium, 1mg/kg body weight. Direct

laryngoscopy was performed 60 seconds after injection of rocuronium and trachea was intubated within 15 seconds with proper size flexometallic endotracheal tube.
Hemodynamic parameters (HR, SBP, DBP and MAP) were recorded for statistical analysis at induction, laryngoscopy & intubation and at 02 minutes interval post laryngoscopy and intubation till 08 minutes.

**Results**

The values obtained were statistically analysed using unpaired student's t-test and unknown population variance assumed unequal. Mean age of the patients were 34.80 years in Group I and 37.66 years in Group II. The difference was statistically insignificant. Mean weights of the patients were comparable in both the groups. Approximately 2/3 of the total cases were male in both the groups as shown in table 1.

**Table 1:** Comparison of Demographic parameters

| **Parameters** | **Group I** | **Group II** |
|---|---|---|
| **No. of patients** | **30** | **30** |
| Age (years)<br>Mean<br>Range | <br>34.80±14.61<br>18-65 | <br>37.66±15.27<br>18-65 |
| Weight (kg)<br>Mean<br>Range | <br>46.60±12.71<br>40-70 | <br>52.00±12.82<br>45-70 |
| Sex%<br>Male<br>Female | <br>20 (66.66)<br>10 (33.33) | <br>21 (70.0)<br>09 (30.0) |

P >0.05 (Not significant)

The doses of propofol for induction recorded in Group I and Group II were compared with the bolus dose of propofol as used by other workers mentioned in this study. The doses of propofol required for induction were 1.30 mg/kg and 1.70 mg/kg in Group I and Group II respectively. The percentages of reduction in the doses of propofol were 35% and 15% respectively as compared to standard bolus dose of propofol, 2mg/kg used in current practice. (Table 2) The profile of propofol doses is as shown in figure 1.

**Table 2:** Comparison of doses of propofol in Group I and Group II

| **Method of administration of propofol** | **Dose of propofol ( mg/kg)** | **Reduction in the dose of propofol (mg/kg)** | **Reduction in the dose of propofol (%)** |
|---|---|---|---|
| **Standard practice:** Propofol bolus | 2.00 | - | - |
| **Group I:** Propofol infusion + Midazolam premedication, 0.02 mg/kg | 1.30 | 0.70 | 35% |
| **Group II:** Propofol infusion | 1.70 | 0.30 | 15% |

**Profile of propofol doses in mg/kg body weight**

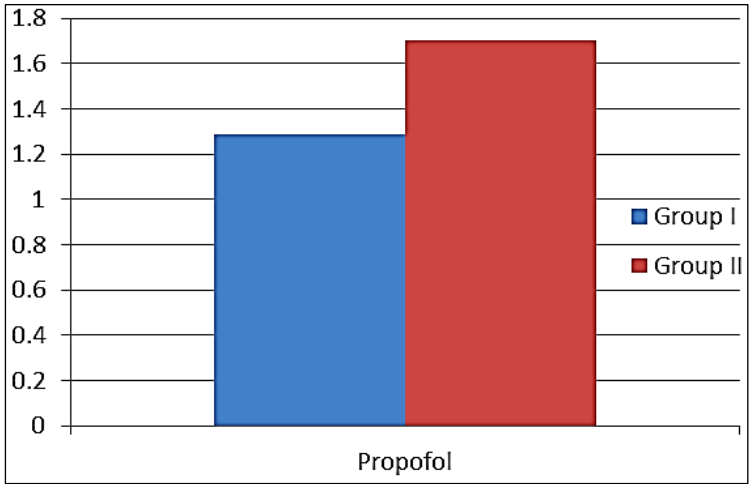


**Fig 1** The reduction in mg/kg dose of propofol in Group I as compared to Group II was 0.4 mg/kg i.e. 20%. The reduction was statistically significant. (Table 3)

**Table 3:** Comparison of doses of propofol in Group I & Group II

| Group | Midazolam (mg/kg) | Propofol dose | | |
|---|---|---|---|---|
| | | Dose of propofol required (mg/kg) | Reduction as compared to Group II (mg/kg) | Reduction % as compared to Group II |
| Group I | 0.02±0.00 | 1.30±0.19 | 0.40 | 20 |
| Group II | - | 1.70±0.24 | - | - |

P< 0.001 (significant)

On comparison of haemodynamic parameters between Group I and Group II, the changes in Heart rate, SBP, DBP and MAP were comparable and statistically insignificant (tables 4-7 & figures 2-5).

**Table 4:** Changes in mean Heart Rate (beats/min)

| Period | Mean±SD | |
|---|---|---|
| | Group I | Group II |
| Preoperative baseline | 87.35±93.54 | 84.15±90.25 |
| Premedication (15 minutes) | 88.07±91.41 | 82.67±90.03 |
| Premedication (25 minutes) | 84.31±8.59 | 83.47±8.33 |
| Preinduction (30 minutes) | 84.07±8.71 | 82.35±8.04 |
| At Induction | 84.09±8.59 | 81.23±8.09 |
| Laryngoscopy & Intubation | 87.69±8.66 | 88.83±5.39 |
| 02 Minutes | 86.43±8.08 | 88.11±5.58 |
| 04 Minutes | 85.49±7.98 | 87.95±5.26 |
| 06 Minutes | 84.47±7.31 | 86.43±5.04 |
| 08 minutes | 85.35±7.37 | 86.09±5.93 |

By student's t-test p>0.05 (not significant)

**Comparison of changes in mean Heart Rate (beats per minute) in Group I & II**

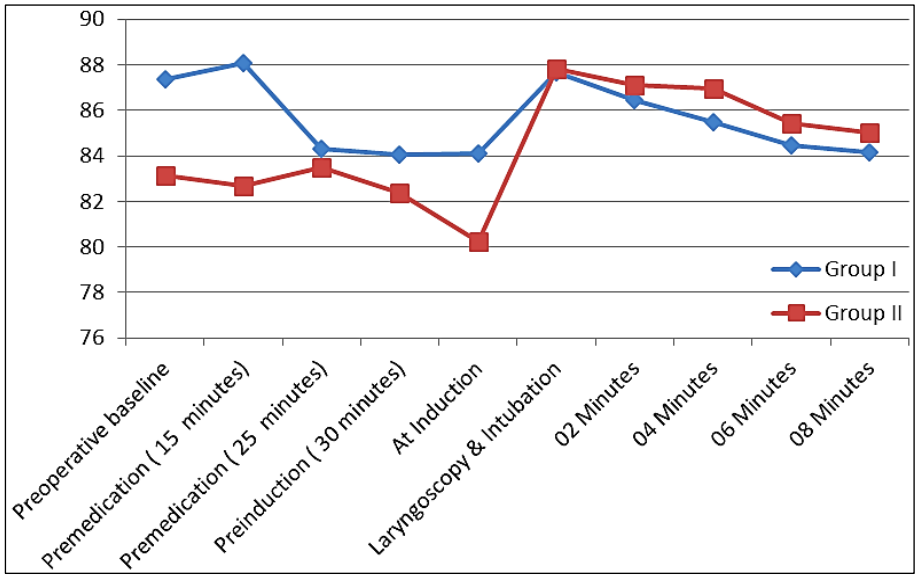


**Fig 2**

**Table 5:** Changes in Systolic Blood Pressure (mmHg)

| Period | Mean±SD | |
|---|---|---|
| | Group I | Group II |
| Preoperative baseline | 124.88±9.41 | 128.48±12.90 |
| Premedication (15 minutes) | 124.32±8.29 | 127.24±8.39 |
| Premedication (25 minutes) | 123.52±9.51 | 126.40±8.51 |
| Preinduction (30 minutes) | 122.36±9.01 | 125.68±8.57 |
| At Induction | 121.04±8.45 | 124.64±8.64 |
| Laryngoscopy & Intubation | 126.92±11.10 | 130.72±8.51 |
| 02 Minutes | 124.80±8.40 | 129.00±8.60 |
| 04 Minutes | 124.24±8.18 | 128.52±7.79 |
| 06 Minutes | 123.24±8.13 | 127.44±8.10 |
| 08 minutes | 122.80±8.09 | 125.44±8.21 |
| By student's t-test | p>0.05 (not significant) | |

**Comparison of changes in mean Systolic Blood Pressure in Group I & II**

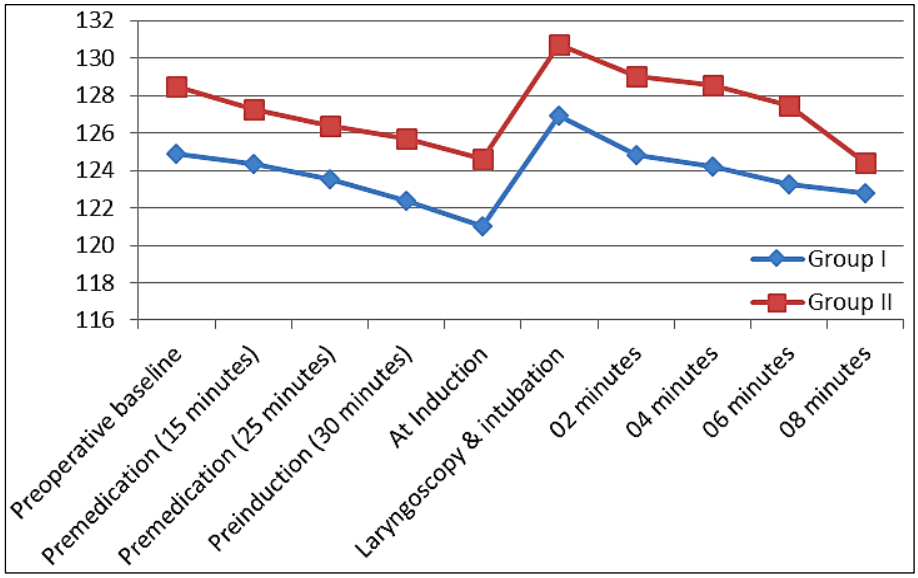


**Fig 3**

**Table 6:** Changes in Mean Diastolic Pressure (mmHg)

| Period | Mean ± SD | |
|---|---|---|
| | **Group I** | **Group II** |
| Preoperative baseline | 78.36±6.92 | 78.44±7.94 |
| Premedication (15 minutes) | 76.60±7.80 | 76.60±6.76 |
| Premedication (25 minutes) | 76.36±6.45 | 76.40±7.01 |
| Preinduction (30 minutes) | 75.84±6.53 | 76.12±6.76 |
| At Induction | 74.48±6.49 | 75.16±6.28 |
| Laryngoscopy & Intubation | 79.68±6.50 | 80.72±5.89 |
| 02 Minutes | 77.44±7.22 | 79.32±6.00 |
| 04 Minutes | 76.16±8.32 | 78.56±5.94 |
| 06 Minutes | 75.64±7.35 | 77.52±5.71 |
| 08 minutes | 75.48±7.80 | 76.64±5.89 |
| By student's t-test | p>0.05 (not significant) | |

**Comparison of changes in mean Diastolic Blood Pressure in Group I & II**

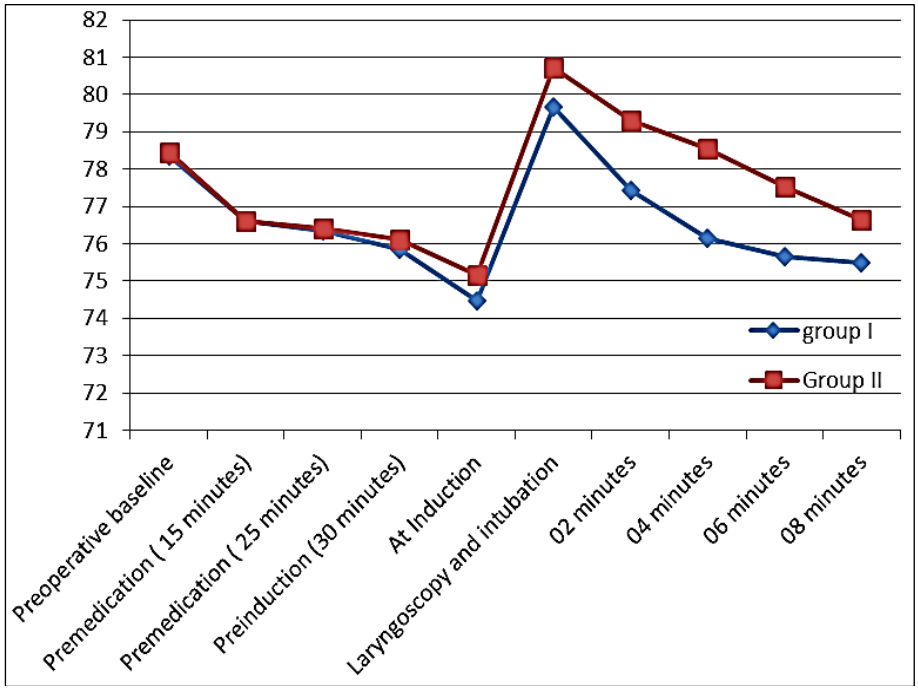


**Fig 4**

**Table 7:** Changes in mean Mean Arterial Pressure (mmHg)

| Period | Mean±SD | |
|---|---|---|
| | **Group I** | **Group II** |
| Preoperative baseline | 92.53±5.72 | 94.79±7.82 |
| Premedication (15 minutes) | 92.17±6.33 | 93.15±5.79 |
| Premedication (25 minutes) | 91.75±5.44 | 92.73±6.02 |
| Preinduction (30 minutes) | 91.01±5.55 | 92.31±6.90 |
| At Induction | 89.67±5.32 | 91.32±5.43 |
| Laryngoscopy & Intubation | 95.09±6.15 | 97.05±4.73 |
| 02 Minutes | 92.89±5.55 | 95.55±5.19 |
| 04 Minutes | 91.85±6.40 | 94.88±5.94 |
| 06 Minutes | 91.17±5.79 | 93.83±5.21 |
| 08 minutes | 90.92±6.07 | 92.57±5.20 |
| By student's t-test | | p>0.05(not significant) |

**Comparison of changes in mean Mean Arterial Pressure in Group I & II**

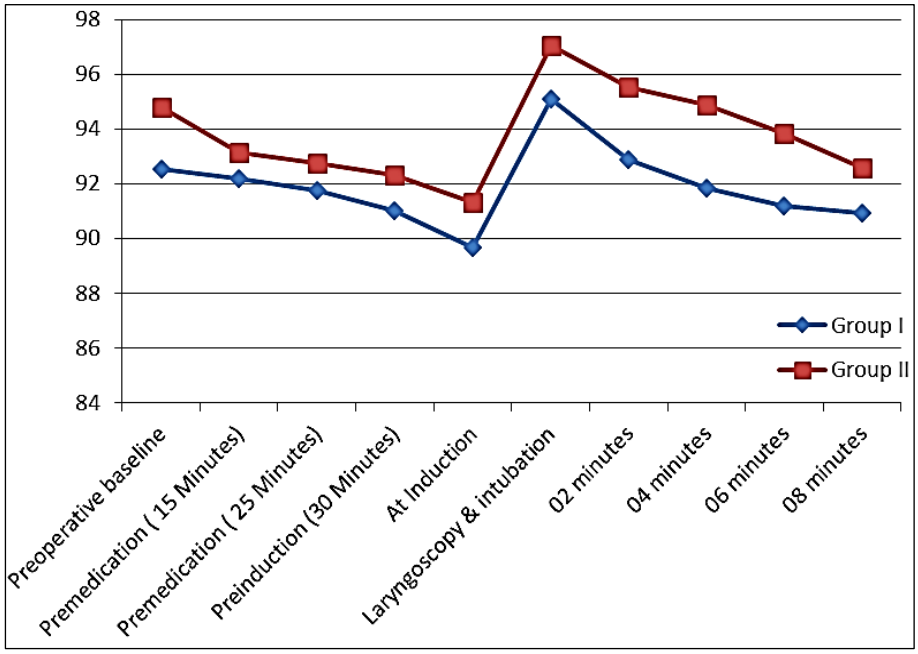


**Fig 5**

## Discussion

Although propofol is a popular anaesthetic agent used for rapid and smooth induction of general anaesthesia with minimal hemodynamic changes, it can cause remarkable hypotension in geriatric and dehydrated patients [8]. It is also known to cause hypotension with concomitant use of opioids & benzodiazepines especially in patients with cardiovascular compromise [9].

Drug combinations are often tried in the practice of anaesthesia to reduce side effects mainly by reducing doses of individual drugs by synergism [4, 5, 6, 10]. The dose of propofol for induction of general anaesthesia depends on several variables. Some of the important variables widely studied by many investigators are rate of injection, age of the patient, use of premedication and multiple anaesthetic end points viz. Loss of verbal contact, dropping of infusion flex (motor), loss of reaction to painful stimuli (antinociception) and attainment of EEG burst suppression [11].

The dose of propofol for induction of anaesthesia ranges from 1.5 to 2.5 mg/kg in unpremedicated healthy adults [12]. But in standard practice, 2mg/kg body weight is the average dose of propofol used for induction of general anaesthesia. Several workers have observed that midazolam premedication decreases dose of propofol for induction of anaesthesia [13, 14].In elderly patients who are premedicated with midazolam, the dose of propofol required for induction is shown to be 1.2 mg/kg. This is an effective and reliable method of reducing propofol dose as shown by Cressy DM et al. [15].Several studies are carried out to study the effect of propofol infusion on the dose requirement for induction of anaesthesia. The dose of propofol for induction is reduced when given by infusion as well [7, 16].In this study, induction was carried out with propofol infusion at the rate of 200 ml/hr i.e.33.3 mg/minute and 'loss of verbal contact' was taken as the end point of induction for both the group of patients.

All patients in both the groups were premedicated with Inj. glycopyrrolate 0.004 mg/kg and Inj fentanyl 0.002 mg/kg intravenously 30 minutes prior to induction.
Group I which was considered as study group received injection midazolam 05 minutes before induction with propofol infusion at the rate of 33.3 mg/min. Effect-site equilibration time of midazolam ranges from 54 seconds to 5.6 minutes [17].Hence, midazolam was given 05 minutes before induction of anaesthesia in this study for the convenience of statistical analysis. Group II also received propofol infusion at the rate of 33.3 mg/min for induction but premedication with midazolam wasn't carried out. The analysis of observations and results was as described in subsequent paragraphs:

The baseline values of age, sex and weight in both the groups were comparable as shown in table 1.

The average dose of propofol in Group I was 1.30±0.19 mg/kg. The average dose of propofol required for induction in Group II was 1.70±0.24 mg/kg as shown in table 2.
The percentages of reduction in propofol doses as compared to bolus dose (2 mg/kg) observed in both the groups of this study were as follows (Table 2):

a) 2mg/kg bolus Vs 1.30 mg/kg in Group I-35%.
b) 2mg/kg bolus Vs 1.70 mg/kg in Group II-15%.

Further on comparison of reduction in the dose of propofol required for induction in Group I versus Group II, the reduction in dose of propofol in Group I was 0.40 mg/kg i.e. 20 %.
(Table 3)

In this study, the difference in hemodynamic parameters between the two groups from premedication till 8 minutes post laryngoscopy and intubation was statistically insignificant (Tables 4-7 & Figures 2-5). The findings correlated well with the studies already carried out on the subject.

## Conclusion

The dose of propofol for induction of general anaesthesia decreased significantly when administered as intravenous infusion after midazolam premedication without significant hemodynamic changes. Propofol infusion with midazolam premedication is recommendable for induction of general anaesthesia in vulnerable patients for maintenance of hemodynamic stability.

## Financial support and sponsorship

Nil.

## Conflict of interest

Nil.

## References

1. Characteristics of Anaesthetic Agents Used for Induction and Maintenance of General Anaesthesia-Medscape-Oct 15, 2004.
2. Khurram Saleem Khan, FCAI FJFICMI, Ivan Hayes, FCAI FJFICMANZ, Donal J Buggy, MD M.Sc. DME FRCPI FCAI FRCA, Pharmacology of anaesthetic agents I:intravenous anaesthetic Agents, Continuing Education in Anaesthesia critical Care & Pain 2014;14(3):100-105.
3. Singh J. Midazolam as an induction agent in comparison with propofol as a safe and effective alternative. Journal of Institute of Medicine Nepal 2013; 34(1):25-32.
4. Ju Deok Kim et al. Hemodynamic Effects of Co-administration of Midazolam during

Anaesthesia Induction with Propofol and Remifentanil in hypertensive Patients. Kosin Medical Journal 2017; 32:36-46.
5. Butt MN, Ahmed A. The Induction Dose of Propofol with Ketamine-Propofol and Midazolam-Propofol Co-induction. J Anesth Clin Res 2013; 4:371.
6. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. Br J Anaesth 1991; 67(5):539-45.
7. Stokes DN, Hutton P. Rate-dependent induction phenomena with propofol: implications for the relative potency of intravenous anaesthetics. Anaesth Analg 1991; 72(5):578-83.
8. Salma Sophie. Anaesthesia for the elderly patient. The journal of the Pakistan Medical Association 2007; 57(4):196.
9. Gill PS, Shah J, Ogilvy A. Midazolam reduces the dose of propofol required for induction of anaesthesia and laryngeal mask airway insertion. Euro J Anaesthesiol 2001; 18(3):166-170.
10. McCLUNE S et al. Synergistic Interaction between Midazolam and Propofol. British Journal of Anaesthesia 1992; 69:240-245.
11. Wilder-smith OH, Ravussin PA, Decostered LA, Despland PA, Bissonnette B. Midazolam premedication reduces propofol dose requirement for multiple anaesthetic end points. Can J Anaesth 2001; 48(5):439-45.
12. Robert K Stoelting. Pharmacology and Physiology in Anaethetic Practice (3rd edition): Nonbarbiturate Induction Drugs, 140-157.
13. Lai HC, Hung CJ, Tsai YS, Wu CC, Lau HK, Tso HS. Co-administration of midazolam decreases propofol dose during anaesthesia in endoscopic laryngeal microsurgery. Acta Anaesthesiol sin 1996; 34(4):191-6.
14. Malik, R., Nandal, Naveen and Gupta, Prakhar. (2021), The Impact of online shoppers to price and quality: a survey study in Delhi-NCR, Efflatounia, 5 (2), pp. 376 – 389.
15. Anderson L, Robb H. A comparison of midazolam co-induction with propofol predosing for induction of anaesthesia. Anaesthesia 1998; 53(11):1117-20.
16. 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(2):108-13.
17. Masago K et al. Success rate of anaesthesia induction using target controlled infusion of propofol with fentanyl. The Japanese journal of Anaesthesiology 1999; 48(3):256-259.
18. Robert K. Stoelting: Pharmacology and Physiology in Anaesthetic Practice (3rd edition): Benzodiazepines, 126-140.