Propofol Autocoinduction and Midazolam Co-induction for Propofol Induction

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ABSTRACT

Introduction: The problem with induction during anaesthesia is decrease in blood pressure, apnea which could be detrimental to patient. Coinduction and autocoinduction are one of the modalities that are developed to overcome hypotension during induction. The study was carried out to observe heart rate, blood pressure response and propofol consumption following midazolam as co-induction or propofol autocoiniduction for propofol induction.

Methods: This study was a conducted in 52 patients of ASA I and ASA II undergoing elective surgical procedures with general anesthesia. Patients were randomly allocated and group P received 0.5 mg/ kg of propofol and group M received 0.04 mg/ kg of midazolam intravenously as autocoindution and coinduction respectively.

Results: The two groups were identical regarding age, weight, ASA status and base line vitals. This study showed that there was significant difference between 2 groups in terms of blood pressure. Decrease in blood pressure from baseline is more in Midazolam group compared to propofol. In terms of Heart Rate there was no statistically significant between two groups at any time of observation. Decrease in HR from baseline was almost similar in both groups. Consumption of Propofol was not statistically significant different between two groups. Propofol group required 8% lesser Propofol than Midazolam group.

Conclusions: Our study concluded that blood pressure was decreased significantly in Midazolam group compared to Propofol group but heart rate was decreased almost similar in both groups and was not statistically significant. Consumption of Propofol was not statistically significant but Propofol group had 8 % lesser Propofol consumption than Midazolam group.

INTRODUCTION

Induction during general anesthesia could be achieved by using intravenous agent or inhalational agent. Problems that are encountered during induction include hypotension, apnea etc., which could be detrimental to patient. Co-induction and autocoinduction are one of the modalities that are developed to overcome hypotension during induction. Auto-coinduction, also known as priming technique, is a technique of giving pre-calculated dose of induction agent prior to giving full dose of same induction agent and priming principle has been studied in relation to muscle relaxant. Goal of

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priming is to reduce side effect and for fast onset of action. The technique in relation to induction agent aims at utilizing sedative, anxiolytic & amnesic properties at sub hypnotic dosage of induction agent when given prior to induction.¹

Co- induction is the practice of administrating a small dose of sedative or other anesthetic agents to reduce the dose of induction agent which improves the ratio of desired versus adverse effects and reduces the cost of expensive drugs such as Propofol.² Midazolam is a benzodiazepine with potent amnesic effect than sedation. Induction dose causes greater decrease in systemic blood pressure and increase in heart rate. Most significant side effect of midazolam is depression of ventilation caused by decreased in the hypoxic drive. Onset of action is 30 to 60 sec.³ Propofol is an intravenous sedative – hypnotics which produces unconsciousness within 30 seconds after rapid intravenous injection. The more rapid return of consciousness within minimal residual central nervous affects is one of the most important advantages of Propofol. Propofol is presumed to exert its effect by selectively modulating Gamma Amino Butyric Acid [GABA] receptor.4

The induction dose of Propofol is 1.5 to 2.5 mg/ kg intra venous with blood level of 2 to 6 ug/ml. It also depends on the associated medications and the patient's age.⁵ Major disadvantage of rapid induction with Propofol is considerable decrement in systemic arterial blood pressure and its high cost. Decrease in systemic arterial blood pressure of 26-28%, diastolic blood pressure 19% and 11% decrease in mean arterial pressure without change in stroke volume and cardiac output was observed when patient induced with 2 mg/kg of Propofol.⁶

Propofol and Midazolam is commonly used combination for induction and it shows interaction for hypnosis and reflex sympathetic suppression. Propofol priming is also effective method of achieving anxiolysis prior to induction of anesthesia and resulted in reduction in dose of Propofol required to induce anesthesia compared to our expected dose as well as avoiding use of another drug.⁷

METHODS

A Prospective, randomized, comparative study was conducted on 52 patients admitted to op-

erating rooms, postoperative ward, post-anaesthesia care unit and wards of Bir Hospital, Kathmandu Nepal. Following Institutional Review Board approval, a written informed consent was obtained from all the patients meeting the inclusion criteria and not having any of the exclusion criteria before enrollment in the study. The inclusion criteria were ASA I and II adult patients of either sex, age 18 to 65 years, all elective surgery under general anesthesia with endotracheal intubation. Exclusion in the study included patients who refused, patients with allergy to the study drug, patients taking analgesics or opioids in last 24 hours before surgery, patients taking sedatives within last 24 hours before surgery, patients with problems with communication, patient with Cardiac arrhythmia, patient with cardiac ischemia.

One day prior to the day of surgery, preoperative evaluation of the patients were done. It included detail history, physical examination and relevant laboratory investigations of the patient. Consent was taken and were explained about possible side effects that may be produced by study drugs. The patient were kept nil per oral from midnight. No premedication was given. On arrival of the patient in the operating room, non-invasive monitors like non-invasive blood pressure with interval setting, electrocardiography, and pulse-oximeter was attached. Patient was cannulated with an appropriate size cannula into the forearm vein. After securing I.V. line Pethidine 0.5mg/kg was given to the entire patient in both groups.

The patient was randomly allotted into one of the two groups by lottery method. The midazolam and propofol groups were written in the piece of paper and kept in sealed envelope. Total of 52 envelope was kept in container. Anesthetic assistant was allowed to take out envelope one at a time before study is being carried out. According to the group written in envelope that is picked out, the drugs were prepared .Drugs were given by the observer that is involved in the study. Patients were blinded to the study drugs given. Propofol used was Provive and midazolam used was Sedoz. Both drugs were manufactured by Claris lifescience in India. The patient was randomly allocated into two groups. The patients in I (P) group received 0.5mg/kg of propofol and group II (M) received 0.04mg/kg of midazolam. One min after the co-induction agent patient was induced by Propofol 40mg bolus then 10 mg every 10 seconds until the loss of eye lashes reflex. Face mask was applied tight at this point and if there was any response to the placement of mask additional bolus of propofol 10mg was given. The study was completed at this point before the intubation and maintenance of anesthesia.

After study was completed, intubating dose of vecuronium was given and inhalation agent was started. After patient was fully paralyzed, intubated with appropriate size of cuffed oral endotracheal tube and fixed after confirmation of endotracheal tube in correct position. Anesthesia was maintained with oxygen plus isofluorane. Vecuronium was used for maintenance muscle relaxation. Ventilation was maintained with intermittent positive pressure ventilation. At the end of the surgery, inhalation agent was stopped and observed for spontaneous respiration. After spontaneous respiration, patient was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.012mg/kg. Gentle suctioning was done before extubation. After extubation, Patient was shifted to post anesthetic care unit.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) was recorded pre-operatively, 1minute after co induction, after induction at 2 minutes and 5 minutes. Total dose of propofol required to induce patient was also recoded. Statistical test was applied for the comparison and P value <0.05 was considered significant. Any complications either with the drug or procedure was managed with the standard hospital protocol.

RESULTS

The gender of patient was compared using chi square test. The age and weight of the patients were compared using student t test. Data were considered to be statistically significant if p value was < 0.05. As shown in Table 1, minimum age in midazolam group was 28 years and maximum 49 years with mean age of 39.00 years and a standard deviation of 5.734 years. In propofol group the minimum age was 20 years and maximum 50 years with mean age of 35.54 years and standard deviation of 10.428 years. There was no significant age difference between the two groups with a p value of 0.144.

Among the 52 patients, there were 8 male and 18 female patients in midazolam group. There were 16 female and 10 male patients in propofol group with no significant difference between 2 groups. The minimum weight in midazolam group was 40 kg and maximum 80 kg with a mean weight of 57.77 kg and a standard deviation of 7.033 kg and the minimum weight in propofol group was 50 kg and maximum of 76 kg with mean age of 54.81 kg with standard deviation of 12.319. There were no significant weight differences between midazolam and propofol groups (p value of 0.292). All the patients in both of the groups were ASA I so both of the groups were comparable. As there were no significant differences in age, sex, weight, ASA physical status of patients between the two groups, both of the groups were comparable.

Table 1	Demographic	distribution:
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Group	Midazolam	Propofol	Р
			value
Age in years	39.00 ± 5.734	35.54 ± 10.428	0.144
(mean ± SD)			
Sex (M/F)	8/18	10/16	0.569
ASA I	26	26	1.0
Weight in kg	57.77 ± 7.033	54.81 ± 12.319	0.292

In this study, baseline HR in midazolam group was 86.04 bpm and in propofol group was 85.88 bpm. At 1 minute after co-induction HR in midazolam group was 82.46 bpm and in propofol group is 80.81 bpm. It was not statistically significant between 2 groups at 1 min after co-induction. At 2 min after induction HR in midazolam group is 79.31 bpm and in propofol aroup was 78.27 bpm. At 2 min, there was not statistically significant between 2 groups. At 5 min after midazolam HR is 76.40 bpm and in propofol group is 76.47 bpm and was not statistically significant between 2 groups. Decrease in HR from baseline at 5 min is similar in both groups. propofol group has similar hemodynamic stability to midazolam group in terms of HR.

Table 2 Comparison of HR between the groups:

Timing	Midazolam	Propofol	Р
			value
Baseline HR	86.04 ± 12.45	85.88 ± 8.96	0.959
HR at 1 min	82.46 ± 11.88	80.81 ± 8.759	0.570
after			
co-induction			
HR at 2 min	79.31 ± 11.46	78.27 ± 8.345	0.710
after			
induction			
HR at 5 min	76.40 ± 12.58	76.47 ± 8.28	0.994
after			
induction			

Baseline SBP in midazolam group is 127.42 mm of Hg and in propofol group is 128.54 mm of Hg .At 1 minute after co-induction SBP in midazolam group is 119.23 mm of Hg and in propofol group is 119.85 mm of Hg. it is not statistically significant between 2 group at 1 min after co-induction. Change in SBP from baseline at 1min was statistically significant in both group. At 2 min after induction SBP in midazolam group is 104.19 mm of Hg and in propofol group was 112.46mm of Hg. At 2 min, there was statistically significant between 2 groups. Change in SBP from baseline at 2 min was statistically significant in both groups. Decrease in SBP is greater in midazolam group than in propofol group. At 5 min after midazolam SBP is 97.50 mm of Hg and in propofol group is 109.65 mm of Hg and is statistically significant between 2 groups. Similarly change in SBP from baseline at 5 min in both groups was statistically significant. Decrease in SBP from baseline at 5 min is greater in midazolam group than propofol. Propofol group has better hemodynamic stability than midazolam group in terms of SBP.

Ta	ble	3	Compar	ison of	SBP	between	the	groups

Groups	Midazolam	Propofol	Р
			value
Base line SBP	127.42±10.281	128.54 ± 12.944	0.732
SBP at 1 min	119.23 ± 10.16	119.85 ± 12.40	0.846
after			
co-induction			
SBP at	104.19 ± 11.15	112.46 ± 12.68	0.016
2 min after			
induction			
SBP at	97.50 ± 9.589	109.65± 13.115	0.000
5 min after			
induction			

Baseline DBP in midazolam group is 79.77 mm of

Propofol Autocoinduction and Midazolam Co-induction for Propofol Induction...

Hg and in propofol group is 78.88 mm of Hg .At 1 minute after co-induction DBP in midazolam group is 72.96 mm of Hg and in propofol group is 72.46 mm of Hg. it was not statistically significant between 2 group at 1 min after co-induction. Change in DBP from baseline at 1 min was statistically significant in both group. At 2 min after induction DBP in midazolam group was 64.73 mm of Hg and in propofol group it was 69.27 mm of Hg. At 2 min, there was not statistically significant between 2 groups. Change in DBP from baseline at 2 min was statistically significant in both groups. Decrease in DBP is greater in midazolam group than in propofol group. At 5 min after midazolam DBP is 60.23 mm of Hg and in propofol group is 67.50 mm of Hg and is statistically significant between 2 groups. Similarly change in DBP from baseline at 5 min in both groups was statistically significant. Decrease in DBP from baseline at 5 min was greater in midazolam group than propofol. Propofol group had better hemodynamic stability than midazolam group in terms of DBP.

Table 4	Comparison	of DBP	between the	groups
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Groups	Midazolam	Propofol	Р
			value
Baseline DBP	79.77 ±6.66	78.88 ± 10.91	0.726
DBP at 1 min	72.96 ±9.676	72.46 ± 9.69	0.854
after			
co-induction			
DBP at 2 min	64.73 ±7.79	69.27± 9.96	0.073
after induction			
DBP at 5 min	60.23 ± 7.03	67.50 ± 9.82	0.04
after induction			

In this study baseline MAP in midazolam group was 95.35 mm of Hg and in propofol group was 94.85 mm of Hg. In propofol group at 1 min it was 88.15 and in midazolam group it was 87.96 mm of Hg. P value is not statistically significant between 2 groups at 1 min (p value 0.941). However in both group change in MAP from baseline at 1 min was statistically significant and decrease in MAP was slightly higher in midazolam group. At 2 min MAP in midazolam group was 78.03 mm of Hg and in propofol group it was 83.54 mm of Hg. P value is statistically significant between 2 groups at 2 min (p value 0.03). In both group change in MAP from baseline at 2 min is statistically significant and decrease in MAP is more in midazolam group. At 5 min MAP in midazolam group was 72.73 mm of Hg and in propofol group it was 81.53 mm of Hg. P value is statistically significant between 2 groups at 5 min (p value 0.01). In both group change in MAP from baseline at 5 min is statistically significant and decrease in MAP is more in midazolam group. propofol appear to be more hemodyanamically stable in terms of MAP.

Groups	Midazolam	Propofol	Р
			value
Baseline MAP	95.35 ± 6.87	94.85 ± 10.71	0.842
MAP at	87.96 ± 8.84	88.15 ± 9.69	0.941
1 min after			
co-induction			
MAP at	78.06 ± 7.45	83.54 ± 10.07	0.03
2 min after			
induction			
MAP at	72.73 ± 7.02	81.35 ± 9.81	0.01
5 min after			
induction			

Table 5 Comparison of MAP between the groups

As shown in Table 6, total dose of propofol in Mmidazolam group was 98.96mg with standard deviation of 13.19 and in propofol group was 90.38 with standard deviation of 20.49 with P value of 0.045. Dose was not statistically significant. Mean dose per weight was 1.77 mg/kg in midazolam group. Mean dose per weight was 1.66 mg/kg in propofol group. Propofol group required 8% lesser Propofol than Midazolam group.

 Table 14 Total Dose of Propofol

Group	Midazolam	Propofol	P value
Drug	98.96 ± 11.51	90.38 ± 20.39	0.07

DISCUSSION

Induction during general anesthesia could be achieved by using intravenous agent or inhalational agent. In modern days intravenous anesthesia has replaced inhalational agent. Problems that are encountered during induction include hypotension, apnea etc. This problem during induction could be detrimental to patient. Various modalities have been developed to reduce problem during induction. Co-induction and autocoinduction are the modalities that are developed to overcome hypotension during induction. Rapid emergence from anesthesia and post op recovery of cognitive function as well as Hemodynamic stability is important requirement of modern anesthesia.

In this study fifty two patients undergoing routine surgical procedures under general anesthesia were selected and randomly divided into two groups as group M- Midazolam and P-Propofol group of 26 patients each. The two groups were comparable in terms of age, sex, weight and base line hemodynamic. After delivering intravenous drugs for general anesthesia to the patients due to their vasodilator effects they tend to decrease the Blood pressure and Mean arterial pressure. The extent of the fall depends upon the dose and adjuvant drugs used.

The present study was conducted to evaluate the clinical efficacy of propofol autocoinduction as compared to midazolam Propofol co-induction in terms of reduction in the induction dose of Propofol and better hemodynamic stability in post induction period.

Heart Rate (HR)

In this study, baseline HR in midazolam group was 86.04 bpm and in propofol group was 85.88 bpm. At 1 minute after co-induction HR in Midazolam group was 82.46 bpm and in Propofol group is 80.81 bpm. It was not statistically significant between 2 groups at 1 min after co-induction. At 2 min after induction HR in Midazolam group is 79.31 bpm and in Propofol group was 78.27 bpm. At 2 min, there was not statistically significant between 2 groups. At 5 min after Midazolam HR is 76.40 bpm and in Propofol group is 76.47 bpm and was not statistically significant between 2 groups. Decrease in HR from baseline at 5 min is similar in both groups. Propofol group has similar hemodynamic stability to Midazolam group in terms of HR.

Supported by similar study done by U. Srivastava et al⁸ in 2006 among 68 ASA I and II patients undergoing elective surgery under general anesthesia they found that there was a fall in Heart rate in all groups but there was no significant difference in Heart rate between Midazolam and Propofol group. Baseline HR in Midazolam group 90 bpm and in Propofol group it was 87 bpm. After induction it was 82 bpm in Midazolam and 78 bpm in Propofol group.

In study done by N.A. Jones et al⁹ in 60 patient > 70 yars ASA I and II undergoing urological surgery there was decrease in HR in the entire 3

group (Midazolam group, Propofol group and control group). It was not statistically significant in terms of HR in 3 groups at any time of observation similar to our study. Similarly fall in HR from baseline was also not significant. Baseline HR in Midazolam was 72.2 bpm and in Propofol it was 71.1 bpm. Reduction in HR after induction in Midazolam group was 2 bpm and in Propofol was 2.3 bpm.

Systolic Blood Pressure (SBP)

Baseline SBP in Midazolam group is 127.42 mm of Hg and in Propofol group is 128.54 mm of Hg .At 1 minute after co-induction SBP in Midazolam group is 119.23 mm of Hg and in Propofol group is 119.85 mm of Hg. it is not statistically significant between 2 group at 1 min after co-induction. Change in SBP from baseline at 1 min was statistically significant in both group. At 2 min after induction SBP in Midazolam group is 104.19 mm of Hg and in Propofol group was 112.46mm of Hg. At 2 min, there was statistically significant between 2 groups. Change in SBP from baseline at 2 min was statistically significant in both groups. Decrease in SBP is greater in Midazolam group than in Propofol group. At 5 min after Midazolam SBP is 97.50 mm of Hg and in Propofol group is 109.65 mm of Hg and is statistically significant between 2 groups. Similarly change in SBP from baseline at 5 min in both groups was statistically significant. Decrease in SBP from baseline at 5 min is greater in Midazolam group than Propofol. Propofol group has better hemodynamic stability than Midazolam group in terms of SBP.

Propofol reduces BP by reducing vascular smooth muscle tone and total peripheral resistance and also by decreasing sympathetic activity. The lesser fall in Propofol group was probably because of reduction in total induction dose of Propofol after its autocoinduction.

In study done by Katharia R et al¹ in 2010 in 90 patients ASA I and II Scheduled for abdominal surgery there was significantly lesser fall in SBP in Propofol group compared to Midazolam which is similar to our study. There was statistically significant between Midazolam and Propofol group in terms of SBP in post induction period and decrease in SBP from baseline was significant in Midazolam group compare to Propofol group. Baseline SBP in Midazolam group was 124.16 mm of Hg and in Propofol group it was 130.80 mm of Hg. After induction SBP in Midazolam group was 109.86 mm of Hg and in Propofol it was 115.26 mm of Hg.

Diastolic Blood Pressure (DBP)

Baseline DBP in Midazolam group is 79.77 mm of Hg and in Propofol group is 78.88 mm of Hg .At 1 minute after co-induction DBP in Midazolam group is 72.96 mm of Hg and in Propofol group is 72.46 mm of Hg. it was not statistically significant between 2 group at 1 min after co-induction. Change in DBP from baseline at 1 min was statistically significant in both group. At 2 min after induction DBP in Midazolam group was 64.73 mm of Hg and in Propofol group it was 69.27 mm of Hg. At 2 min, there was not statistically significant between 2 groups. Change in DBP from baseline at 2 min was statistically significant in both groups. Decrease in DBP is greater in Midazolam group than in Propofol group. At 5 min after Midazolam DBP is 60.23 mm of Hg and in Propofol group is 67.50 mm of Hg and is statistically significant between 2 groups. Similarly change in DBP from baseline at 5 min in both groups was statistically significant. Decrease in DBP from baseline at 5 min was greater in Midazolam group than Propofol. Propofol group had better hemodynamic stability than Midazolam group in terms of DBP.

In study done by Katharia R et al¹ in 2010 in 90 patients ASA I and II Scheduled for abdominal surgery, there was significantly lesser fall in DBP in Propofol group compared to Midazolam which is similar to our study. Baseline DBP in Propofol group was 79.3 mm of Hg and in Midazolam group it was 79.96 mm of Hg. Post induction DBP in Propofol group is 74.64 mm of Hg and in Midazolam group it was 65.03 mm of Hg. There was statistically significant between Midazolam and Propofol group in terms of DBP in post induction period and decrease in DBP from baseline is significant in Midazolam group compared to Propofol group.

Mean arterial pressure (MAP)

In this study baseline MAP in Midazolam group was 95.35 mm of Hg and in Propofol group was 94.85 mm of Hg. In Propofol group at 1 min it was 88.15 and in Midazolam group it was 87.96 mm of Hg. P value is not statistically significant between 2 groups at 1 min (p value 0.941). However in both group change in MAP from baseline at 1 min was statistically significant and decrease

in MAP was slightly higher in Midazolam group. At 2 min MAP in Midazolam group was 78.03 mm of Hg and in Propofol group it was 83.54 mm of Hg. P value is statistically significant between 2 groups at 2 min (p value 0.03). In both group change in MAP from baseline at 2 min is statistically significant and decrease in MAP is more in Midazolam group. At 5 min MAP in Midazolam group was 72.73 mm of Hg and in Propofol group it was 81.53 mm of Hg. P value is statistically significant between 2 groups at 5 min (p value 0.01). In both group change in MAP from baseline at 5 min is statistically significant and decrease in MAP is more in Midazolam group. Propofol appear to be more hemodyanamically stable in terms of MAP.

In study done by Srivastava U et al¹⁰ in 2006 among 68 ASA I and II patients undergoing elective surgery under general anesthesia they found that there was no significant difference between Propofol and Midazolam group in terms of MAP. Baseline MAP in Midazolam group is 92 mm of Hg and post induction value is 80 mm of Hg which was 13 % fall from baseline. Baseline MAP in Propofol group is 95 mm of Hg and post induction value is 84 mm of Hg which is 11 % fall from baseline. Fall in MAP in Midazolam is greater than that of Propofol but is statistically not significant. The result is bit different from our study probably because study was carried out in patient undergoing general, orthopedic or gynecological patient and control group was taken for the study. Fentanyl was used as analgesic, verbal response was used as end point. Propofol induction was performed after 2 min of co-induction and 30 mg Propofol was used every 10 second for induction.

Dose of Propofol

The dose of Propofol required to induce anesthesia depends on several variables – end point used, age of patient, rate of injection and use of premedication. The induction dose ranges from 2 to 2.5 mg/kg when given as bolus in young patient to 1.2 mg/kg when given to elderly premedicated patient induced with slow 300 ml/hr.⁷

In this study Mean dose of Propofol in Midazolam group was 98.96mg and in Propofol group was 90.38. Propofol group required slightly lesser amount of Propofol than Midazolam group and is not statistically significant. Propofol group required 8% lesser amount of Propofol than Midazolam group. In the study done by Anil Kumar A et al⁶ there was 27.48 % reduction in induction dose requirement of Propofol after Propofol autocoinduction. In their study they have compared control group with Propofol group but in our study Midazolam group was compared with Propofol group. The amnestic and sedative action of Propofol at sub hypnotic dose may facilitate the induction of anesthesia at lower induction dose of Propofol.¹

However, in the study done by Katharia R et al¹, reduction in the induction dose requirement of Propofol was maximal in Midazolam group compare to Propofol group but statistically not significant. In their study they have compared Midazolam Propofol co-induction and Propofol autoco-induction with control group (saline group). Mean Propofol induction dose in Midazolam group is 60.7 mg and in Propofol group was 75.7 mg. Both group showed statistically significant difference observed in Propofol induction dose requirement compared to control group. There was 45.37 % lesser in Midazolam group and 31.88% lesser in Propofol group compared to control group. Midazolam and Propofol act synergistically and Midazolam pretreatment decreases induction dose of Propofol. It would have been better if control groups were used in our study. They have used BIS value of 45 as end point of Propofol induction whereas we have used eyelash reflex as end point. It may have effect in dose requirement. In their study they have taken age group of 18 to 50 year however we have taken up to 65 years.

CONCLUSION

On conclusion, this study showed Propofol autocoinduction to Propofol induction was better in terms of blood pressure decrease. In terms of heart rate decrease, there is not much difference between two groups. Consumption of Propofol for induction was not significant between Propofol and Midazolam group but was 8% lesser in Propofol group which is clinically significant.

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