International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 2; February 2018; Page No. 01-05

A study of propofol auto-co-induction versus midazolam-propofol co-induction using priming principle by bispectral index analysis for ambulatory surgery

[1] Dr. Krupali, [2] Dr. Bhavna Soni, [3] Dr. Pragna Vachhrajani
[1] PG, Department of Anaesthesiology, Smimer, Surat, Gujarat, India
[2] Associate professor, Department of Anaesthesiology, Smimer, Surat, Gujarat, India
[3] Professor and Head, Department of Anaesthesiology, Smimer, Surat, Gujarat, India

Abstract
Aims and objective: This study was performed to evaluate whether "priming principle" applied for induction dose of propofol which will affect the total dose requirement and thereby favorably influences peri intubation hemodynamics. And also to compare the recovery criteria in propofol auto-co-induction and midazolam–propofol co-induction in ambulatory surgery.
Method: The study was carried out on 90 patients of ASA I and II physical status, aged 18-55 years, undergoing ambulatory surgeries under general anaesthesia, who were randomly divided into three groups of 30 patients each: Group PP (Propofol-Propofol) received 0.5 mg/kg propofol IV, group MP (Midazolam-Propofol) received 0.05 mg/kg midazolam IV and group C (Control) received 3 ml of normal saline 3 minutes before induction. All patients were induced with Inj propofol 2 mg/kg until BIS value reaches to 45-50 (Speed of Injection is 30 mg/ 10 sec).
Results: The total requirement of propofol to maintain BIS between 45-50 during induction was decreased in both the study group compared to control group ($P<0.05$) but more reduction (26%) was seen in midazolam co-induction group ($P<0.001$) compared to auto co-induction group (17%) ($P<0.05$). While hemodynamic stability and early discharge was observed in propofol auto-co-induction group.
Conclusion: In day care anaesthesia, propofol auto-co-induction appears to be a safe alternative technique to midazolam-propofol co-induction looking to overall reduction in propofol requirement and discharge time from hospital.

Keywords: propofol, priming principle, ambulatory surgery

Introduction
Ambulatory surgery is growing rapidly worldwide. A primary goal for ambulatory anesthesia is rapid recovery from anesthesia leading to rapid patient discharge with minimal side effect [1]. Delayed or complicated recovery from general anesthesia can have a considerable impact on patient safety, patient satisfaction, recovery room resources, and cost of patient care. Post-operative pain, nausea and vomiting are common causes for delayed patient discharge and un-planned hospital admission [1]. Faster recovery and reduction of time spent in the post anesthesia care unit (PACU) and ambulatory surgery unit (ASU) can accelerate operating room turn over and reduces cost.
Induction agent, Propofol has a good safety record, but relatively expensive. In ambulatory surgery, Propofol despite its cost has become popular to facilitate rapid patient recovery. When it is used as the sole induction agent; it causes significant decrease in arterial blood pressure and cardiac output [2]. So, various methods [3] are tried to reduce the dose requirements of induction agents like 1) concurrent use of nitrous oxide, opioid, barbiturate and benzodiazepines i.e. Midazolam, 2) Augmentation with local and regional anesthesia and 3) Use of 'Priming Principle'; 'co-induction'.
"Auto co-induction" is a technique of giving a pre-calculated dose of induction agent prior to giving the full dose of same induction agent. This technique is also known as the "Priming technique". In this technique 20% of the ED_{95} or about 10% of the intubating agents are administered 2-4 min prior to administering the second large dose of induction [4].
"Co-induction" is defined as concurrent administration of two or more drugs prior to induction of anesthesia [4]. By using these Principles, induction dose requirement is reduced considerably with less adverse hemodynamic effect.

Method
After approval from institutional ethical committee, the study was conducted in 90 patients of ASA I and II physical status, aged 18-55 years, undergoing ambulatory surgeries under general anaesthesia. Patients were randomly divided into three groups of 30 patients each: Group PP (Propofol- Propofol) received 0.5 mg/kg propofol IV, group MP (Midazolam-Propofol) received 0.05 mg/kg midazolam IV and group C (Control) received 3 ml of normal saline. On arrival at recovery room, all patients were enquired about NBM status. Intravenous line was secured and Inj. DNS was administered at a rate of 10ml/kg/hr. Vital parameters were taken. All patients were pre-medicated with Inj. Ranitidine 1 mg/kg and Inj. Ondansetron 0.15 mg/kg intravenously 30min before surgery.
In operation theatre, monitoring of Pulse, Mean arterial BP, SpO2 and BIS value were noted. Two readings were taken 5 min apart before induction of anaesthesia and average was

taken as baseline parameter for the study. All patients were pre-oxygenated with 100% oxygen by face mask for 3 minutes and Inj. Glycopyrrolate 8-10µg/kg + Inj. Fentanyl 1µg/kg were given intravenously slowly.

According to study group assigned, priming agent was given intravenously. After 3 minutes of priming, all patients were induced with Inj propofol 2 mg/kg until BIS value reaches to 45-50 (Speed of Injection is 30 mg/ 10 sec) and inj. succinylcholine 1.5-2 mg/kg IV to facilitate oral endotracheal intubation. Anaesthesia was maintained with O_2 + N_2O + Inj. Vecuronium (0.1 mg/kg) IV + Isoflurane using close circle absorber system with IPPV mode (Intra-operatively, maintain BIS between 40 -60).

Following dose was calculated

- Priming dose of midazolam or propofol according to weight of the patients.
- Induction dose of propofol to achieve BIS value of 45-50.
- Total dose of propofol.

Following parameters were observed

- Intra operative monitoring:
  - Intra operatively, Pulse rate, Mean BP, SpO_2 and BIS value were recorded at post priming interval, immediately after induction, immediately after intubation, 5 minutes and 10 minutes after intubation.
  - Duration of surgery and type of surgery were noted.
- Post-operative monitoring: Following parameter were observed at every 15 min interval for 1 hour and then at 90 min and 120 min:
  - Pulse, Mean BP, SpO2,
  - VAS for postoperative pain,
  - Modified observer's alertness scale,
  - Bellville score for nausea & vomiting,
  - Richmond agitation score,

Post anaesthesia discharge scores (PADS) +clinical discharge criteria (CDC) for home readiness was noted every 1 hourly till score reaches ≥ 9.

Results

The statistical analysis was done by student t-test for inter group comparison and ANOVA test for intra group comparison. Significance of P value was suggested as follows: 'P' Value was >0.05 insignificant. 'P' Value was <0.05 significant.

'P' Value was < 0.001 highly significant.

i) Demographic Data

Demographic data like age, sex, duration of surgery were comparable in all the three groups (P>0.05). 52.22% surgeries were laparoscopic surgeries. Mean duration of surgery was 83.83±24.07 min in group PP, 82.66±27.78 min in group MP and 78.53±24.76 min in group C, which were statistically comparable (p>0.005).

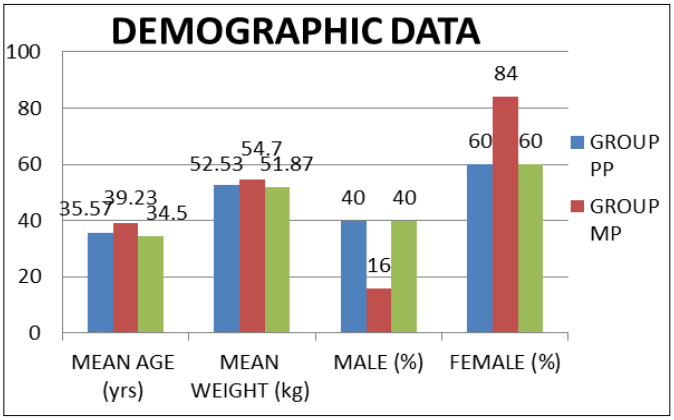

Fig 1

Chart showing duration of Surgery

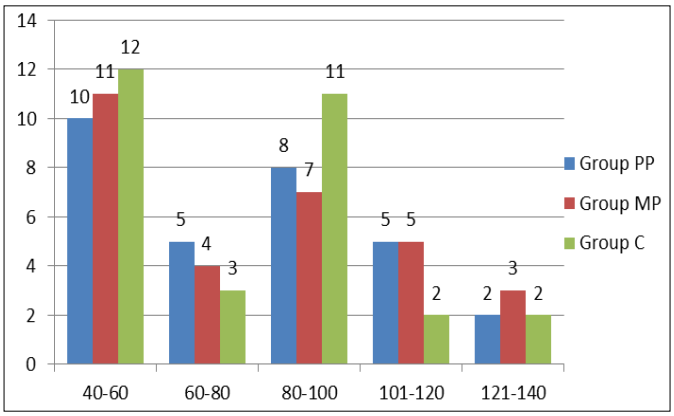

Fig 2

ii) Total Dose Requirement of Propofol

In present study, **total requirement of propofol** to maintain BIS between 45-50 during induction was decreased in both the study group compared to control group, which was statistically highly significant, but reduction in dose requirement of propofol was more in midazolam co-induction group (26%) compared to propofol auto-co-induction group (17%) which was statistically significant (P<0.05).

Table 1

	(MEAN±SD)	(MEAN±SD)	P value
Group PP v/s MP	87.53±13.32	80.16±11.92	P<0.05
Group PP v/s C	87.53±13.32	107.33±11.72	P<0.001
Group MP v/s C	80.16±11.92	107.33±11.72	P<0.001

Chart showing total induction dose requirement of Propofol

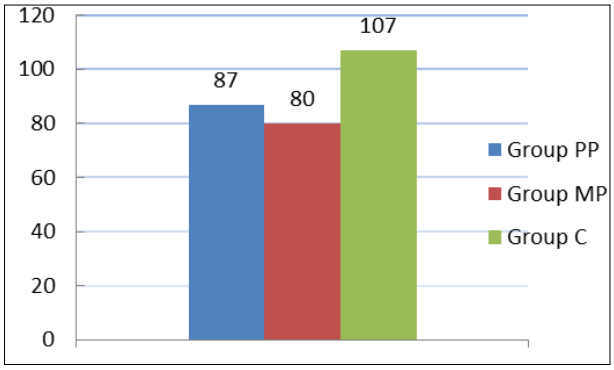

Fig 3

iii) Mean Pulse Rate

In present study, **basal mean Pulse rate** was 85.33±11.14 per min, 87.06±7.82 per min and 85.6±11.10 per min in group PP, group MP and group C respectively were comparable and there was no statistically significant difference observed in all three groups (P>0.05).

At the post priming interval, fall in mean pulse rate was observed (but no bradycardia was observed, pulse rate <60/min) in group PP (81.23±11.66) and group MP (86.43±11.14), which was statistically highly significant (P<0.001) compared to control group (91.56±11.38).

Immediately after induction, fall in mean pulse rate was observed among the all three groups which was statistically significant (P<0.05). But statistically highly significant reduction was observed in group PP (75.76±9.82) as compared to group MP (82.66±7.5) and group C (85.4±10.36) (P<0.001).

While immediately after intubation, there was rise in pulse rate in all three groups but least rise was found in the propofol auto-co-induction group (75.76±9.82), which was statistically highly significant (P<0.001).

At 5 min and 10 min interval after intubation, no significant change in mean pulse rate was observed in all three groups.

Chart showing pulse rate (per minutes)

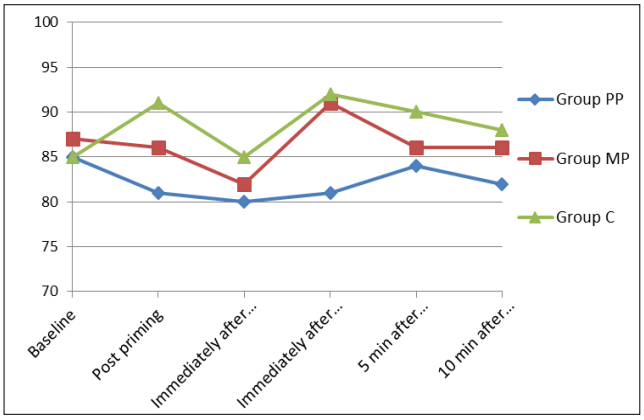

Fig 4

iv) Mean Arterial Blood Pressure

In present study, **baseline Mean Arterial Blood Pressure** was 93.66±7.53 mm of Hg, 96.43±9.32mm of Hg and 95.46±8.6mm of Hg in group PP, group MP and group C respectively which were statistically comparable (P>0.05).

At **post priming interval**, change in mean arterial pressure was statistically insignificant (P>0.05) in all groups.

Immediately after induction, more fall in mean arterial pressure was observed in group C (85.83±6.7) which was statistically significant (P<0.05) compared to group PP (90±6.56) and highly significant compared to group MP (93.53±8.26) (P<0.001). While fall in arterial pressure was statistically insignificant in group PP compared to MP (P>0.05). But no hypotension was observed and no drug intervention was required.

Immediately after intubation, rise in mean arterial pressure (but no hypertension >113) was observed in all three groups from baseline value to post intubation period, but least rise in mean arterial pressure was observed in group PP which was statistically highly significant (P<0.001) as compared to group C and statistically significant (P<0.05) as compared to group MP. There was no significant change in mean arterial pressure from baseline value to post intubation period in midazolam co-induction group as compared to control group.

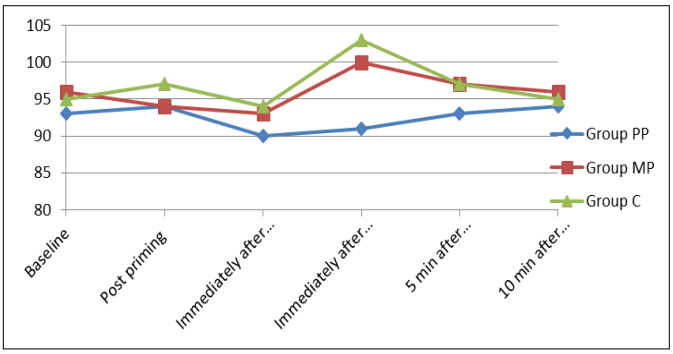

Fig 5

v) BIS value

Baseline mean BIS value was 97.03±1.42 in group PP, 97.03±1.43 in group MP and 96.76±1.5 in group C, which was comparable in all three groups (P>0.05).

At post-priming interval, maximum fall in BIS value was observed in propofol auto-co-induction group as compared to other two group (P<0.001). While reduction in BIS value was statistically highly significant (P<0.001) in group MP compared to group C.

Immediately after induction, there was statistically highly significant reduction in BIS value in Group PP and Group MP as compared to Control group (P<0.001).While comparing between group PP and group MP, there was more fall in BIS value was noted in group PP which was statistically significant(P<0.05).

Thereafter, no statistically significant change was observed in BIS value (P>0.05).

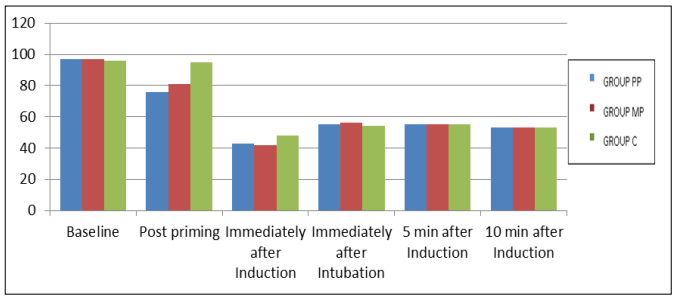

Fig 6

vi) Alertness and Sedation Score

Assessment of alertness by **modified observer's score** was done and less alertness was observed in midazolam co-induction group compared to group PP and group C, which may be the reason for delayed home discharge. In Propofol auto-co-induction group, patients can be discharge home earlier as compared to midazolam group and control group.

Postoperatively up to 45 min, **Richmond agitation sedation score** was statistically significantly high at any time interval ($P<0.05$) in group MP (0.16±0.37). So, more sedation was observed in midazolam group.

Postoperatively, immediately after extubation, mean **VAS** was 0.86±1.45 and 1.33±2.05 in group PP and group MP respectively compared to group C 1.6±2.06, which was statistically highly significant ($P<0.001$). But patient does not demand analgesic.

vii) Discharge Score

There was no significant difference observed in discharge score postoperatively up to 1 hour between three groups ($P>0.05$). Patient in group PP had higher mean discharge score at 3 hours (8.6±0.4) compared to group MP (8±0.4) and group C (8±0.1), which was statistically significant ($P<0.05$).At 4 hours, in group PP mean discharge score was (9±0), in group MP (8.3±0.5) and in group C (9±0), which was statistically highly significant ($P<0.01$).So, patients of control group and Propofol auto-co-induction group could be discharged to home earlier (4hr) as compared to midazolam group (5hr).

Discussion

Day surgery is a cost-effective, quality approach to surgery that has expanded rapidly in recent years. The advantages of day case surgeries are mainly to patient and hospital. They include minimal psychological disturbances for the patient especially children, economical with reduced requirement of nursing and medical supervision and also advantage to hospital services allowing more number of patients to be treated and finally consequent reduction in the risk of hospital-acquired infection and venous thrombo-embolism (VTE) [5, 6].

Shorter acting anaesthetic agents e.g. Propofol and monitors e.g. BIS (bispectral array) and EEG have been used which significantly reduces the hospital stay. If BIS is maintained between 45-65, lesser anaesthetics are required without intra-operative awareness with faster recovery and reduced postoperative complications thus early hospital discharge.

In day care anaesthesia, various methods are tried to reduce the induction dose requirement of anaesthetic agent like Propofol i.e.

1) Priming principle
2) Use of nitrous oxide, opiod, barbiturates and benzodiazepines
3) Augmentation with local anaesthetic or magnesium sulphate

In present study, to reduce the anaesthetic agents requirement (1) priming principle was applied to induction agent propofol either by co-induction using midazolam or auto-co-induction by propofol itself and (2) BIS guided anaesthesia was administered to all patients.

We calculated the total requirement of induction agent, Propofol to maintain BIS between 45 -50. The mean induction dose requirement of Propofol was 87.53±13.32 mg in group PP, 80.16±11.92mg in group MP and 107.33±11.72 mg in group C.

So, we observed that the total requirement of propofol to maintain BIS between 45-50 during induction was decreased in both the study group compared to control group (107.33±11.72mg) ($P<0.05$) but more reduction was seen in midazolam co-induction group (80.16±11.92mg) compared to auto co-induction group (87.53±13.32 mg) ($P<0.001$). Djaiani [7] and Anderson [8] with their colleague carried out a study and observed that combination of midazolam and propofol and propofol auto-co-induction reduces induction dose of propofol. Results of other studies [4, 9] are consistent with our study.

Co-induction results from a combination of both pharmacodynamic interaction at a receptor level and pharmacokinetic effects related to the distribution of the induction agent. The mechanism of action of co-induction drugs like propofol and midazolam is to reduce anxiety and the associate sympathetic response. Both propofol and midazolam act on common receptor, GABA receptor. Thus, potentiating the each other's effect. So, combination of propofol-midazolam is synergistic when used in commonly expected dose range, which reduces the induction dose of propofol.

Propofol is known to produce sedation and anxiolysis at low doses. Initial administration of priming dose of propofol (0.5 mg/kg) is thought to produce anxiolysis, sedation and thereby reduces associated sympathetic drive and the induction dose to produce hypnosis. In day care anaesthesia, the major disadvantage of rapid induction with propofol is associated with considerable fall in systemic arterial blood pressure as it reduces sympathetic activity, the vascular smooth muscle tone and total peripheral resistance. Priming principle applied to induction agent, propofol may reduce this side effect.

Several other studies [4, 10, 11] measured a changed in hemodynamic measures following propofol 2.5 to 3 mg per kg and found that MAP decreased by 22-33% from the baseline. In present study, immediately after induction, significant fall in MAP was observed in control group (85.83±6.7 mm of Hg) compared to group PP (90 ± 6.56 mm of Hg) and group MP (93.53±8.26 mm of Hg). The lesser fall in group PP was because of reduction in total induction dose of propofol after auto-co-induction (87.53±13.32 mg). Fall in MAP was dose dependent when used propofol for induction of anaesthesia.

In group MP, the small but statistically significant fall in mean

arterial B.P. at post induction interval (93.53±8.26 mm of Hg) was due to the amnesic, anxiolytic and synergistic action of midazolam with propofol. These factors reduce the total dose of induction agent, propofol.

Rise in mean arterial pressure after intubation in all three groups was due to stress response produced by laryngoscopy and endotracheal intubation. But least rise in MAP was observed in group PP, which was due to reduction in the sympathetic drive, cardiac output and reduced induction dose of propofol. Propofol pre-treatment does not completely attenuate reflex sympathetic stimulation secondary to intubation, but it is definitely more advantageous than the other two groups.

In present study baseline mean BIS value was comparable in all three groups At post priming interval, fall in BIS values was observed in group PP(23%) and group MP(17%) compared to group C(2%)which was statistically highly significant (P<0.001). The BIS Index reflects the reduced cerebral metabolic rate produced by most hypnotics and sedative drugs. BIS titrated anaesthesia with clinical judgment reduces anaesthetic consumption without awareness lead to slightly quicker awakening.

In present study, more sedation (1.2=0.66) in patients of midazolam group than propofol group (0.46+0.57) was observed. Sedation by midazolam was mediated by α_1 receptor and elimination half life of drug is 1-4 hours. While subhypnotic dose of propofol provides sedation and amnesia and its elimination half life is 30-60min. So patients can be discharge from hospital earlier in propofol auto-co-induction group compared to midazolam co-induction group. Djaiani and his colleagues observed that discharge time in midazolam co-induction group was more than propofol auto-co-induction group and control group[7].

Conclusion

Propofol–propofol auto-co-induction appears to be a safe alternative to midazolam–propofol, which reduces overall propofol requirements and improves discharge times from hospital.

1. Priming with midazolam (co-induction) or propofol (auto-co-induction) significantly reduces the induction dose requirement of propofol to maintain bispectral index between 45-50 in BIS guided anaesthesia.
2. Pre-dosing with midazolam (co-induction) is more effective than pre-dosing with propofol (auto-co-induction) in requirement of induction dose of propofol with advantage of cardiovascular stability but delayed recovery and discharge to home due to sedation in day care surgeries.
3. By using priming principle and BIS guided anaesthesia, we can discharge the patients early (within 4 hours) in propofol auto-co-induction group, while it is delayed in propofol-midazolam group (within 5 hours).

References

1. Spencer SL. Effects of bispectral index monitoring on ambulatory anaesthesia. Anaesthesia, 2004; 101:2.
2. Amatya A,1 Marhatta MN, A Comparison of Midazolam Co-induction with Propofol Priming in Propofol Induced Anesthesia J Nepal Health Res Counc. 2014; 12(26):44-8.
3. Anil kumar A, Sanikop CS, Kotvr PF. Effect of priming principle on induction dose requirement of propofol-A randomized control trial. IJA. 2006; 50(4):283-287.
4. Roopam Katria, Ajay Singhal, Sukirti Prakash, Ishwan Singh. A comparative study of efficacy of propofol auto co-induction versus midazolam propofol co-induction using priming principle. IJAnaesth. 2010; 54(6):558-561.
5. Gangadhar SB, Gopal TMS, Paramesh KS. Rapid emergence of day-care anaesthesia: A review. Indian J Anaesth, 2012; 56:336-41.
6. Jyoti Mallikarjuna, Purneema K. Co-induction: A comparative study of midazolam, ketamine and propofol as coinducing agents to propofol.
7. Djaiani G, Ribes-Pastor MP. Propofol auto-induction as an alternative to midazolam co-induction for ambulatory surgery. Anaesthesia 1999; 54:63
8. Anderson J, Robb H. A comparison of midazolam co-induction with propofol predosing for induction of anaesthesia. Anaesthesia, 1998; 53:1117-29.
9. Jones NA, Elliott S, Knight J. (Anaesthesia 07/2002; 57(7):649-53) A comparison between midazolam co-induction and propofol pre-dosing for the induction of anaesthesia in the elderly
10. Cressy DM, Claydon P, Bhaskaran NC, Reilly CS. Effect of midazolam pretreatment on induction dose requirement of propofol in combination with Fentanyl in younger and older adults. Anaesthesia, 2001; 56:108-13.
11. Sanket H Mehta, Pinalben G Dabhi, Golwala MP, Upadhyay MR. Effect of priming Principle on the induction dose Requirement of Propofol. Int J Res Med. 2015; 4(1):69-73.