e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(4); 622-627

Original Research Article

Effect of Priming Dose of Propofol and Midazolam Co Induction on the Clinical Efficacy during Induction of Anesthesia: A Randomized Interventional Study

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Received: 25-01-2024 / Revised: 23-02-2024 / Accepted: 26-03-2024
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Conflict of interest: Nil

Abstract:

Objectives: Priming principle or auto-co-induction refers to administration of a small calculated dose of a drug before giving the total dose. The main objective of our study was to compare dose reduction of Propofol and hemodynamic changes during the peri intubation period among the patients who were given propofol auto-co-induction and midazolam propofol co-induction, while applying priming principle.

Methodology: A total of 90 patients with the American Society of Anesthesiologists (ASA) physical status class I/II who were scheduled to undergo elective surgeries under general anesthesia were randomly divided into three groups of 30. Group P received Propofol (0.5 mg/kg), Group M received Midazolam (0.05 mg/kg) and Group N received Normal Saline (3cc). It was succeeded by intravenous induction with Propofol in all patients of three groups. We compared the total dose of Propofol in all three groups required to achieve the BIS value of 45. Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Oxygen saturation and any associated complication was recorded.

Results: The induction dose requirement of Propofol in Group P (Propofol auto co induction) and Group M (Midazolam co induction) were found to be significantly ($p<0.01$) lesser than Group N (Controls). Among the groups with priming dosage use, the mean induction dose was found to be lesser in Group M (115.67 mg ± 11.50) than Group P (125.50 mg ± 10.03). The hemodynamic parameters like SBP, DBP and heart rate were found to be significantly more variable in Group M than other two groups ($p<0.01$). No consequences or complications of drug administration such as nausea, vomiting or hypotension etc. were reported in any of the patients.

Conclusion: Priming with Propofol and Midazolam co-induction was effective in reducing the total induction dose of Propofol. Dose reduction of Propofol was significantly higher in Midazolam primed group as compared to Propofol primed group. However, Propofol auto-co-induction group had reported better hemodynamic stability in peri intubation period.

Keywords: Propofol, Efficacy, Priming principle, Midazolam, Co induction.

Introduction

Induction of anesthesia is a pivotal step in anesthesiology as it is generally associated with variations in hemodynamics and altered physiology of various body systems. [1] Day care procedures including surgery have become popular modality of treatment throughout the world. Since, prolonged length of hospital stay due to anesthetic drugs has been found to be associated with increased morbidity and mortality leading to significant economic burden and risk of hospital acquired complications. Nowadays propofol is preferred as induction agent due to its properties of smoother and more rapid induction, rapid awakening & orientation times, clear headed recovery, decreased incidence of post-operative nausea vomiting better intubating conditions & upper airway integrity. [2,3] However, literature shows that Propofol is associated with major decline in systemic arterial pressure due to decrease in cardiac output and systemic vascular resistance. [4] Various research studies demonstrated that with the simultaneous use of opioids, benzodiazepines (Midazolam), nitrous oxide, barbiturates (Thiopentone), amplification with local anesthetics or use of 'auto-co-induction' leads to decrease in the total induction dose of Propofol. [5-10] Similarly with muscle relaxants,

applying the concept of priming or auto-co-induction means that a small sub-paralyzing dose of non-depolarizing muscle relaxant (20% of the ED95 or about 10% of the intubating when given a few minutes prior to induction. [11,12] " Co-induction" on the other hand is administering two or more drugs simultaneously to facilitate the induction of anesthesia by synergistic action of the two drugs. [13,16,17] Due to synergistic action of Propofol and Midazolam on reflex sympathetic suppression and hypnosis, studies have reported reduction in the total dose of Propofol (up to 50%) when used as co-induction. The co-induction was found to be safe in terms of maintaining hemodynamic stability and recovery profile of patients. [18-20] Application of "priming principle" or using sub hypnotic dose of Propofol due to its anxiolytic effect has also been reported. [11] The present study aims to compare the clinical efficacy in terms of dose reduction of Propofol when used as priming dose in one group and Midazolam co-induction in another group and analyzing the results with a control group. We also compared the hemodynamic parameters of patients in three groups.

Material and Methodology

This was a prospective randomized double blinded study conducted after obtaining approval from the Institutional ethics committee (NBE/2017/14242-43). Sample size of this study was calculated using epi info software, considering a power of 80% and α of 0.05. Sample size was 30 in each group. After taking the written informed consent from all the patients, they were randomly (computer generated numbers) allocated into three groups (30 in each group): Group P- Propofol, Group M -Midazolam, Group N- Normal saline. A total of 90 patients were included in the study.

Inclusion Criteria: Patients in the age group of 18-60 years of either gender, belonging to ASA grade I &II, scheduled for surgery under general anesthesia, who give consent for participation in the study

Exclusion Criteria: Patients with any significant neurological, hematologic, cardiac or renal disorders or those with known allergy to study drug (or its constituent), patients allergic to egg (or egg proteins), pregnant women, patients with disorder of involuntary movements and patients taking medications for psychiatric illness, were excluded from the study.

One day prior to surgery, whole procedure was explained to the patients and preanesthetic evaluation was done. All the consented patients were kept nil by mouth for at least six hours before surgery. On the day of surgery, in the operating room, the routine monitoring of the patient in the terms of pulse oximetry, non-invasive blood pressure (NIBP), continuous surface ECG and Bi Spectral Index (BIS) were recorded. Before the induction of anesthesia, heart rate (HR) and blood pressure (BP) were recorded as baseline pre-operative values after taking an average of two consecutive readings (5 minutes apart). An intravenous line with 20 Gauge cannula, appropriate for the surgical procedure was secured. 15 minutes before induction of anesthesia, patients were pre-medicated with glycopyrrolate 4mcg/kg IV.

- Group P- received the priming agent IV Propofol 0.5mg/kg
- Group M- received IV Midazolam co-induction 0.05mg/kg
- Group N- received IV Normal saline 3 cc [control group]

Two minutes later, IV induction with propofol in all the patients in three groups was done until the BIS value of 45 was achieved. The speed of injecting IV propofol (induction dose) in all cases was at the rate of 30mg/10 seconds. Following this, relaxation and intubation was achieved using Atracurium 0.5 mg/kg IV and anesthesia was maintained on O2 (45%) /N2O (55%), inj. Fentanyl 2 μg/kg, Sevoflurane as inhalational agent and inj. Atracurium (0.1 mg/kg) as intermittent bolus dose.

The parameters recorded were: Total dose of propofol required to achieve BIS value of 45.

HR, SBP (Systolic Blood pressure) and DBP (Diastolic Blood pressure) were measured just before induction (baseline), immediately after induction, immediately after intubation, and 5 minutes after intubation.

Any complications during this period were noted.

Statistical analysis: Data was collected and entered into Microsoft Excel version 10 (Microsoft Corporation, NY, USA). All statistical calculations were done using SPSS software version 21, using unpaired "t" test and Man Whitney U test. A 'p' value of <0.05 was considered as statically significant.

Results

The demographic characteristics and ASA grade of the patients among three groups was comparable, as shown in Table 1.

Table 1: Demographic details and ASA classification of patients in three groups

Parameter	Group P, n=30 (Propofol)	Group M, n=30 (Midazolam)	Group N, n=30 (Normal saline)	p value
Age (Mean± SD)	44.6 ± 10.57	44 ± 11.74	41.63 ± 10.74	0.547
Gender distribution M:F	16:14	16:14	14:16	0.837
Weight in kg (Mean± SD)	57.63 ± 5.58	56.7 ± 6.11	57.77 ± 6.65	0.746
ASA Grade I:II	22:8	21:9	22:8	0.529

SD: Standard deviation; M:F: Male: Female; ASA: American Society of Anesthesiologist. The induction dose requirement of Propofol was found to be significantly lower ($p<0.01$) in Group P and Group M as compared to Group N. Mean induction dose of Propofol was found to be 12.7% lesser in Group M (Midazolam co-induction group) and 5.2% lesser in Group P (Propofol priming or auto-co-induction group) as shown in Table 2.

Table 2: Dose of Propofol used in three groups

Parameter	Group P, n=30 (Propofol)	Group M, n=30 (Midazolam)	Group N, n=30 (Normal saline)	p value
Dose of Propofol in milligram (Mean ± SD)	125.50 ± 10.03	115.67 ± 11.50	132.50 ± 10.57	<0.01

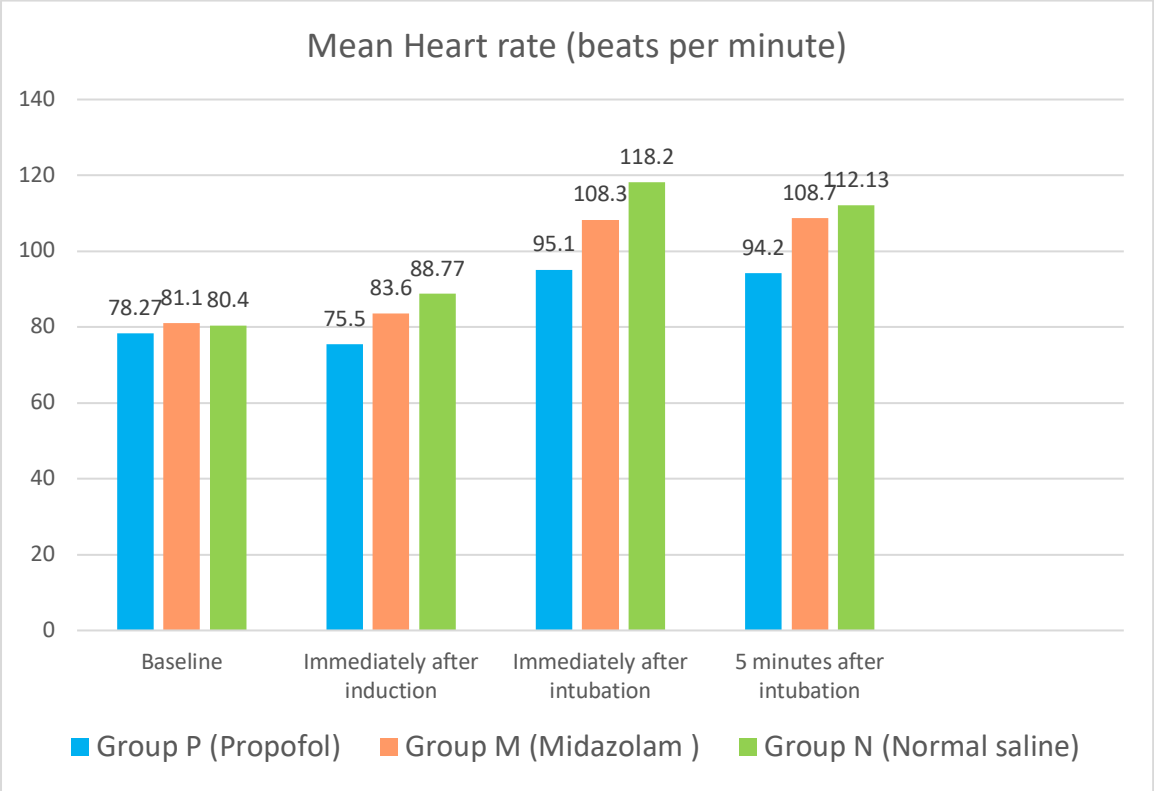

Figure 1: Comparison of heart rate among the patients of three groups

Baseline values of HR were comparable between the three groups. But there were significant variations ($p<0.01$) in the heart rate immediately after induction, immediately after intubation and five minutes post intubation as well. In Group P, there was a significant drop in HR, immediately after induction. However, rise in HR values of all patients were noted after intubation. Oxygen saturation (SpO2) was maintained above 95% during induction, intubation, and during surgery the mean SpO2 values were comparable in the three groups and no significant variability was observed in the levels.

Baseline values of SBP and DBP were comparable between three groups. Immediately after induction, Mean SBP was observed to fall in all three groups, significantly greater in Propofol group and Control group than Midazolam group ($P<0.01$). After intubation, immediate readings of SBP showed rise in all three groups, with maximum rise being observed in Midazolam group (25.4% higher than pre induction value).

This significantly greater rise in SBP was maintained in Midazolam (8.9%) and Propofol (7.7%) group, when the reading was repeated after five minutes post intubation. Mean DBP was observed to fall in all three groups at induction with

a slight fall (0.3%) in Midazolam group and maximum fall in Control group (14.7%). After intubation, maximum rise in DBP (39.3%) was observed in Midazolam group, followed by Propofol group (17.9%) and Control group (7.8%), as shown in table 3.

Table 3: Comparison of Blood Pressure values among the patients of three groups

Blood Pressure (BP) in mmHg ± SD		Group P, n=30 (Propofol	Group M, n=30 (Midazolam)	Group N, n=30 (Normal saline)	p value
SBP	Baseline	117.90 ± 2.63	121.97 ± 1.97	131.13 ± 6.32	0.09
	Immediately After Induction	107.30 ± 2.77	118.50 ± 1.91	116.50 ± 3.14	<0.01
	Immediately After Intubation	132.70 ± 3.06	152.93 ± 1.98	136.63 ± 3.13	<0.01
	5 minutes after intubation	127.10 ± 3.32	132.77 ± 2.13	128.37 ± 3.38	<0.01
DBP	Baseline	71.07 ± 1.36	74.27 ± 1.96	81.97 ± 5.94	0.08
	Immediately After Induction	63.77 ± 1.52	74.07 ± 2.02	69.93 ± 1.95	<0.01
	Immediately After Intubation	83.77 ± 1.72	103.47 ± 2.36	88.37 ± 3.58	<0.01
	5 minutes after intubation	78.53 ± 1.98	82.97 ± 2.46	80.23 ± 3.61	<0.01

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Discussion

Induction is the first stage of a sequential process to transform patient into a temporary state of unconscious ess to facilitate a therapeutic procedure or surgery. Propofol is preferred as induction agent of choice due to its properties of smooth and rapid induction with rapid recovery. However, a major drawback linked with rapid induction by Propofol has been found to be substantial fall in systemic blood pressure due to its action on systemic vascular resistance. [4] "Priming" is giving a smaller dose before giving full dose of a drug and it is well studied concept with the use of non-depolarizing muscle relaxants where priming leads to shortening of onset of neuromuscular blockage and enhancing conditions for intubation as explained by Schwartz et al. [12] A similar priming principle applied to the induction dose of Propofol has been evaluated earlier by Maroof et al. [11]

Another technique called "co-induction" using multiple drugs (two or more) to induce anesthesia has been reported to exhibit synergism with the combined use of induction agents like nitrous oxide, opioids, clonidine, magnesium sulphate and midazolam. [5-9] the potential benefits of synergism in clinical practice imply that anesthesia could be induced with a smaller combined total dose of anesthetic agents with fewer side effects. [16,17]

Cressy et al studied co induction technique with midazolam propofol in 120 patients and found that there was dose reduction when midazolam was used. They observed that midazolam priming was associated with decreased dose requirement of propofol for induction in general anesthesia. [21]

Our study was conducted to compare the clinical efficacy of Propofol auto co-induction or priming (group P) in comparison with Midazolam & Propofol co-induction (group M). We reported a significant reduction in the induction dose of Propofol along with hemodynamic stability in peri-intubation period. In our study, we used BIS as a modality to monitor depth of anesthesia. We took BIS value of 45 as adequacy of depth of anesthesia. So, we considered BIS value of 45 as a target to compare between all three groups.

Demographic Data and ASA Grade: All the patients in three groups were comparable with respect to age, gender and ASA grade.

Induction Dose: Study done by Kataria et al, demonstrated that in group I, whose patients received priming dose (with propofol), had induction dose requirement of propofol as 75.70 mg (19.78 SD). However, mean induction dose of propofol was 60.70 mg (15.74 SD) and 111 mg (31.65 SD) in the in group II (midazolam co-induction) and control group respectively. They observed 31.88% decrease in dose in group I which was primed with propofol and 45.37% decrease in dose requirement in group II which was primed with midazolam.22 In our study, induction dose of propofol was reported to be 115.67 mg (11.5 SD) in Midazolam co-induction group, 125.5 mg (10.03 SD) in Propofol priming group and 132.5 mg (10.57 SD) in the control group patients. There was 12.38% and 5% reduction of Propofol dose in Midazolam co induction group and Propofol primed group respectively, in comparison to the control group. Similar study done by Amatya A et al revealed that the Midazolam co induction group had lowest Propofol induction dose requirement i.e, 80.50 mg, followed by Propofol priming group (105.62 mg) and 111.7 mg in control group. [23] Kumar AA et al have also found a significant reduction in induction dose requirement of propofol after applying the priming principle (propofol auto-co-induction). [10]

Hemodynamic Variations:

Blood Pressure: Literature shows that one of the predominating effects of Propofol is decrease in systemic vascular resistance as well as means arterial pressure, which leads to increased sympathetic activity and rise in heart rate. In our

study, after induction there was an immediate fall in blood pressure (both systolic and diastolic) in all the patients irrespective of the group assigned, with least fall (in SBP and DBP) recorded in Midazolam group, followed by Propofol group patients, who had 8.9% fall in SBP and 10.2% fall in DBP, and then control group patients with 11.1% fall in SBP and 14.6% fall in DBP when compared with baseline values. After intubation, immediate SBP and DBP increased in all patients of three groups. The rise in SBP and DBP was highest in Midazolam group (25% rise), followed by Propofol group with 12.6% rise and 3.8% rise in control group.

This rise in SBP and DBP among Midazolam group of patients was maintained five minutes after intubation too, when second reading was assessed (in comparison to Propofol auto co induction group. Variations in blood pressure (SBP and DBP) were found to be more in the Midazolam group as compared to Propofol group, and this difference was statistically significant. Similar results have been reported by Kataria B et al and Cressy et al, who found that blood pressure readings (SBP and DBP) in Midazolam co induction group showed significant variations as compared to Propofol priming group. [21,22]

Heart Rate: In our study, immediately after induction, there was a slight fall in heart rate of Propofol group patients. After intubation, the immediate heart rate (HR) was reported to have risen in all three groups, with the mean HR rising from 78.27 ± 7.66 to 95.10 ± 7.28 in Propofol group (priming) patients, 81.10 ± 6.21 (baseline HR) to 108.30 ± 6.00 in Midazolam group and from 80.40 ± 6.13 to 118.20 ± 5.63 in Control group. The highest rise was found in the control group with 47% increase, followed by 33.5% rise in Midazolam group patients and 21% rise in Propofol group patients. Similar results were shown by Kataria et al, who reported that post intubation; the heart rate of control group patients was significantly higher than propofol and midazolam group patients. Although there was rise in heart rates of all patients after intubation, but highest rise (31%) was found in control group than midazolam group (20%) and propofol group (27%). [22]

Oxygen saturation (SpO_2): Oxygen saturation values were compared among all three groups . We maintained SpO_2 above 95% throughout the surgery in all groups.

Complications: No complications like nausea, hypotension or bradycardia etc. were noted in any of the patients in either of the groups.

Conclusion

The present study reinforces the benefits of synergism in induction dose reduction of Propofol by technique of “priming” and “co induction”. The greater reduction in dose was found in Midazolam group than Propofol group. However, priming in relation to propofol provides better hemodynamic stability in peri intubation period as compared to midazolam group. Taking into consideration the results of our study, it is eminent that measures to know induction dose of propofol are controversial and difficult to assess. We used BIS value as a measure for dose of propofol. Other measures like loss of verbal command or response to placement of a face mask or loss of eye lash reflex can be used. Further studies with greater sample size and advanced monitoring can help in comparing results and providing better recommendations.

Acknowledgements: We are grateful to the patients who consented to be part of the study.

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