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Effect of Propofol Auto-Co-Induction versus Midazolam Propofol Co-Induction Using the Priming Principle

Praneshwori Sinam[1], Heikham Kenedy Singh[1*], Sanasam Sarat Singh[2], Takhelmayum Hemjit Singh[3], Priyadarshini Sharma Monohar[1] and Maharabam Binarani[4]

[1]Senior Resident, [2]Professor, [3]Associate Professor, [4]Assistant Professor,
Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India

***Corresponding Author:**
Heikham Kenedy Singh
Senior Resident, Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India

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Abstract

Background: Application of priming principle is well documented in relation to the use of muscle relaxants and some recent studies have highlighted the efficacy of priming technique in relation to induction agents. Clinical efficacy in terms of dose reduction and alteration in peri-intubation haemodynamics was compared in propofol auto-co-induction and midazolam propofol co- induction groups along with a control group.

Methods: The study was a prospective, randomized double blinded one carried out in 90 patients scheduled for elective surgeries under general anesthesia, who were randomly divided into three equal groups. Group I received 0.5 mg/kg propofol IV (20% of the pre-calculated induction dose), group II received 0.05 mg/kg IV midazolam and group III received 3 ml of normal saline. This was followed by IV induction with 1% propofol later in all the three groups until the bispectral index value of 40-60 was attained.

Results: A significant (p=0.0000) decrease in induction dose requirement in first two groups but haemodynamic stability during induction and intubation was more in propofol auto-co-induction group.

Conclusion: Pre-dosing with propofol is less effective than midazolam in reducing the dose of propofol to induce anaesthesia with haemodynamic parameters varying significantly in the three groups

Keywords: Priming principle, co-induction, auto-co-induction, propofol, midazolam

Introduction

Induction is one of the most crucial event in Anaesthesiology as it is associated with a number of alternations in haemodynamic and physiology of various body system[1]. Thus, a reduction in the induction dose would reduce the associated side effects. Various methods have been studied for reducing the induction dose requirements of propofol. Priming principle is applied for induction agents to reduce this side effect. It aims at utilizing the sedative, anxiolytic, and amnesic properties. Application of the priming principle is a well known technique with use of non-depolarizing muscle relaxants where it shortens the onset of neuromuscular blockade and provides better intubating conditions. By applying this principle, in relation to propofol, it can be assessed whether it affects the total induction dose requirement and then the consequent dose dependent haemodynamic alternations.[2]

Auto-co-induction [3] is a technique of giving a pre-calculated 10-20% dose of induction agent prior to giving the full dose of the same induction agent; this technique is also known as “the priming technique’’. Propofol, 2,6 – diisopropylphenol, a non-barbiturate anaesthetic agent, is preferred induction agent

nowadays due to its properties of rapid onset of action smooth and rapid recovery ; attenuation of laryngeal , pharyngeal and tracheal reflexes; providing adequate depth of anaesthesia during intubation and also sedative action in intensive

care unit. However, major disadvantage of rapid induction of propofol is the considerable fall in systemic arterial pressure 5 due to reduction in cardiac output and systemic vascular resistance immediately after injection. Then, 2 minute after injection , despite less than normal systemic vascular resistance , due to resetting of the baroreceptor reflex to a small pressure value than normal by propofol, the H.R and S.V are decreased.6 So, studies were undertaken to reduce these side effects and utilize the advantages provided by propofol. The dose of propofol required to induce anaesthesia depends on several variables – the end point used, the age of the patient, the rate of injection and the use of premedication.7 Studies have confirmed the use of BIS monitoring as an objective marker for assessing level of consciousness BIS value of 40-60 is preferred for surgical patients.8

"Co-induction" is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia documenting synergism.,9 Synergism can be achieved with drugs such as barbiturates, benzodiazepines such as midazolam, ketamine, opiods, adrenergic α- agonists, magnesium, esmolol and methylene blue.10 Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression.11 This study was done to evaluate whether the priming technique reduces the effective dose of induction agent and favourably influences the peri-intubation haemodynamics.

Methods

The present study was prospective, randomized, double blinded and controlled one, conducted in a tertiary care centre, Imphal, Manipur, after obtaining approval of the Institutional Ethical Committee. Ninety patients, aged between 18 to 60 years, American Society of Anesthesiologists (ASA) Grade I and II, from both sexes having no history of adverse anaesthetic reaction, were randomly allocated into three equal groups consisting of 30 patients each: group I (propofol), group II (midazolam) and group III (normal saline). Uncooperative and unwilling patient, patient with anticipated difficult intubation, pregnant and lactating women, history of adverse reaction to the study drugs and haemodynamically unstable patients were excluded from the study.

The patients were allocated into three groups based on computer generated randomization as Groups (I, II, III) receiving the priming agent 0.5 mg/kg IV propofol, 0.05 mg/kg IV midazolam or 3 ml of normal saline respectively, followed by titrated IV induction with 1% propofol(in all the three groups) until the BIS value of 40-60 was achieved.

Standard anaesthesia protocol was followed in all the patients. After establishing venous access and standard monitoring, all patients were administered intravenous inj. ranitidine 1 mg/kg, inj glycopyrrolate 10 mcg/kg and inj metoclopromide 150 mcg/kg. In the operation theatre, monitors, i.e., non-invasive blood pressure (NIBP), electrocardiogram (ECG), pulse oximeter; bispectral index monitor (BIS VISTA Monitoring system, Covidien Company, USA, Version-2013) were employed. Pre-operative baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were taken 5 minutes apart before induction of anaesthesia. Baseline BIS value was also recorded. After induction with their respective study drugs, endotracheal intubation was done after giving inj. rocuronium bromide 0.9 mg/kg and anaesthesia was maintained with O2, N2O, sevoflurane and intermittent doses of inj rocuronium bromide. Reversal of neuromuscular blockade was done by inj. neostigmine 0.05 mg/kg and inj glycopyrolate 0.01mg/kg. Any complication during this period, i.e., apnoea, vomiting, laryngospasm, involuntary movements, coughing, or any other complications were also noted. Total dose of propofol required in achieving targeted BIS value of 40-60 were recorded. SpO2, BIS value, HR, SBP and DBP were also recorded just before induction, immediately after induction, immediately after endotracheal intubation, and 5 minutes after intubation.

Sample size was determined based on the study by Kartaria et al,12 where we calculated as 28 in each group, which was rounded to 30 taking into consideration of 5% drop out rate in the study, assuming a power of 80% and α (alpha) value of

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0.05. The data were collected were analysed statistically using the SPSS statistical package (version 21.0). Comparison between the groups for the induction dose and haemodynamic parameters was done using One Way Analysis of Variance (ANOVA) test. A P value of <0.05 was considered to be significant and P<0.001 was considered to be highly significant.

Results

The demographic parameters such as age, weight, gender and ASA grading among the three groups were comparable and statistically not significant, as shown in Table 1.

Table 1. Socio-demograohic details

Groups	Mean age (years)	Sex Distribution M:F	ASA GRADE I:II	Mean body wt. (kg)
I	37.73±12.11	19:11	27:3	55.9±9.7
II	34.77±14.25	22:8	27:3	56.7±8.9
II	35.67±14.66	19:11	25:5	58.5±11.9
P value	0.124	0.638	0.638	0.592

P<0.05 is considered significant

A statistically significant difference (*P*<0.001) was observed in propofol induction dose requirement in groups I and II compared to the control group III. Mean induction dose requirement was found to be 45.33% lesser in midazolam co-induction group and 35% lesser in propofol auto-co-induction group as compared to the control group [Table 2].

Table 2. Mean propofol induction dose requirement in the three study groups.

Groups	Mean induction dose requirement (mean + SD)	One way ANOVA
Group I	72.6 + 17.9	F= 43.0
Group II	62.3 + 18.6	p- 0.0000
Group III	107.6 ± 22.5	

P<0.05 is considered significant

Significant (*P*<0.001) difference was also observed in post-priming BIS values among the three groups. Maximum fall at post-induction interval was found in the midazolam group. However, comparable BIS values at post-induction, post-intubation and 5 minutes post-intubation for propofol auto-co-induction and midazolam co-induction groups [Table 3].

Table 3: Comparison of BIS values among three groups

BIS values	GROUPS			One way ANOVA
	Group I (propofol)	Group II (midazolam)	Group III (normal saline)	
Baseline	97.2±12.5	98.1±14.6	99.2±16.1	F= 0.144 p-0.866
Post-priming	73.4±11.2	80.7±9.9	90.3±13.2	F= 16.2 p-0.000

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Post-induction	43.2±8.9	41.4±7.8	45.2±7.2	F=1.695 p-0.190

P<0.05 is considered significant

Heart rate was observed to fall significantly in the propofol auto-co-induction group at the post-induction interval. Post-intubation rise in the HR was observed in all the three groups but the least rise was found in the propofol group (group I). Mean SBP was observed to be maintained at induction in the control group with a slight fall observed in other two groups. Maximum rise in SBP after intubation from pre-induction value was observed in the propofol co-induction group. Mean DBP was also observed to be maintained in control group at induction (with a slight fall observed in other two groups). Maximum fall in DBP (17.99%) from pre- induction value at post-induction interval was observed in midazolam co-induction group. Maximum rise in DBP (16.80%) from baseline value at post-intubation interval was observed in propofol auto-co-induction group

Discussion

Induction is an important part of general anesthesia being associated with a number of haemodynamic and physiological alternations of various body system. Hence, maintaining haemodynamics stability during induction is very important. In the present study, after pre dosing with 0.5mg/Kg of propofol (Group-I), the mean induction dose of propofol in group I was 72.60±17.9 mg as compared to the mean induction dose of 107.60 ± 22.5 mg in the control group III. There was 35% decrease in induction dose of propofol by auto co-induction with propofol which was similarly observed in the previous studies.12and it was statistically significant. The dose reduction in the propofol group prior to induction dose caused sedation and anxiolysis, thus allowing induction of anaesthesia with lower doses of propofol.13 Kumar AA et al3 also observed the 27% reduction in induction dose requirement of propofol after propofol auto co-induction. Propofol is one of the widely used induction agent but rapid induction with a conventional dose of propofol is associated with fall in the systemic arterial pressure due to reduction in cardiac output and systemic vascular resistance immediately after injection. This decrease in the systemic vascular resistance causes reflex increase in the sympathetic activity which is mediated by the baroreceptors present in the carotid sinus and aortic arch, thereby causing an increase in the heart rate. 2 minutes after injection, despite less than normal systemic vascular resistance, the heart rate and stroke volume are decreased due to resetting of the baroreceptor reflex to a smaller pressure value than normal by propofol .[14]

In group II, after priming with 0.05 mg/kg of midazolam, mean induction dose of propofol was 62.30 mg as compared to the mean induction dose of 107.60 mg in the control group. We noticed a 45.33% reduction in the induction dose of propofol in group – II(p=0.0000) which was consistent with the findings of earlier studies conducted by Cressy DM et al[15] and Welder- Smith OHG et al16 which is probably due to synergistic interaction between the two drugs. Synergism has been found between agents with known functional link in the central nervous system viz, midazolam and propofol acting on a common receptor site, the GABA receptors. The concurrent use of synergistic drugs such as nitrous oxide, barbiturates, benzodiazepines such as midazolam, ketamine, opoids , α-agonist, magnesium, esmolol and methylene blue has been practiced to reduce the inducing dose of propofol and its associated side effects like hypotension, pain on injection, nausea, vomiting,etc.10

Predetermined BIS value (i.e BIS- 40-60) was taken as an end point of induction in our study. Maximum reduction in BIS at post priming interval was found in propofol auto- coinduction group, but contrary to that, mean induction requirement of propofol was maximally reduced in the midazolam co-induction as also observed in earlier study12 as a result of synergism of hypnosis and reflex sympathetic suppression between midazolam and propofol.

The fall in both SBP and DBP in propofol group was significantly little lesser at the post induction period as compared to the other two groups. This may be due to reduction of total induction dose of propofol after its co-induction and associated sympathetic inhibition as also seen in studies carried out by Djaini et al.2 After intubation, rise of H.R was comparable in all the study groups. And, also SBP and DBP

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immediately after intubation and 5 minutes post–intubation were significantly more in all the study groups which was contrary to the previous studies.[12] Laryngoscopy and tracheal intubation is known to increase sympathetic activity as a stress response to the above nociceptive stimuli and therefore, result in increase heart rate and blood pressure.8 Therefore, during peri-intubation period, changes in haemodynamic parameters showed similar trend in all the study groups which was also observed in earlier studies conducted by Srivastava et al 13, Amataya A et al .17

The total incidence of side effects in the three groups viz: hypotension, nausea and vomiting were 10%, 6.6% and 20% respectively in group I, II and III respectively. The incidence of hypotension in the three groups were 0%, 3.3% and 6.7% in group I, II and III respectively. The incidence of hypotension was more in group III, which might be due to larger dose of propofol used in achieving the end point of induction i.e. BIS value of 40-60. This might be due to dose dependent decrease in blood pressure as a consequence of fall in systemic vascular resistance.18Also, the incidence of nausea and vomiting were 10%, 3.3% and 13.3% respectively in the three groups.

In this study, we have observed that midazolam co-induction significantly reduces the induction dose of propofol as compared to propofol auto co-induction. However, there was significantly no effect on haemodynamics and were comparable among all the study groups. We have been unable to demonstrate any clear benefit in terms of improved cardiovascular stability like other studies.[19]

Limitation Of The Study And Future Directions:

More studies with larger samples is required before considering these observations as generalized along with different doses of the priming drug

Conclusions

The present study compared the efficacy of propofol auto-co-induction versus midazolam propofol co-induction. The following conclusions and inferences can be drawn from this study:

1. A significant fall in the induction dose requirement of propofol was found in this study.
2. The priming in relation to propofol provided haemodynamic stability both at post-induction interval and to intubation.
3. Propofol autocoinduction appears to be cost effective by significantly reducing the total dose of propofol.

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