ORIGINAL ARTICLE

Comparative Evaluation of Standard Propofol Induction with Propofol Priming and Midazolam-Propofol Co-Induction in Patients Undergoing General Anesthesia

Hina Kouser, Naine Bhadrala, Anju Jamwal, Urfi Umbreen

Abstract

Background: Propofol has emerged as an induction agent of choice over the past two decades due to its quick, smooth induction and rapid recovery. The main concern for an anesthesiologist is the hemodynamic instability caused by the standard induction dose of propofol (2–3 mg/kg). **Material & Methods:** A prospective randomized, double blind control study was conducted where 120 patients (20-60 years) were divided into 3 groups. Group A received 0.4 mg/kg of propofol injection diluted with Normal Saline to make total amount to 5 ml (priming), Group B received 0.03 mg/kg midazolam injection diluted with Normal Saline to make a total amount of 5ml (co-induction) while as Group C received 5 ml of Normal Saline(control). We compared the total dose of propofol requirement for induction of anaesthesia in all the 3 groups, taking loss of verbal contact as the end point. Total dose and induction dose of propofol is different in all groups as 30 mg propofol is followed y 10 mg increments every 10 seconds till loss of verbal contact. and Additionally, changes in haemodynamic status like blood pressure and heart rate at various intervals were studied and compared among the groups. **Results:** The groups were similar in terms of age, sex, weight and American Society of Anesesthesiologists Physical Status. The dose of propofol required to induce anesthesia was1.77 mg/kg in propofol group, 1.46 mg/kg in midazolam group and 2.87 mg/kg in the control group. There were less hemodynamic changes in midazolam group compared to the other two. **Conclusion:** Co-induction with midazolam is more effective than propofol priming and standard propofol induction in reducing the dose of propofol induced anaesthesia & associated with minimum hemodynamic alterations. From the present study we concluded that propofol priming and midazolam-propofol co-induction significantly decreases the average induction dose of propofol with better hemodynamic stability and least adverse effects. However, the greater decrease in induction dose of propofol and better hemodynamics were seen with the midazolam- propofol co-induction.

Key Words

Propofol, Midazolam, Co-induction, Priming

Introduction

Co-induction has been used to describe the practice of administering a small dose of sedative or other anaesthetic agent to reduce the dose of induction agent required. [1] Synergy occurs when the combination of two drugs with similar properties produces supra-additive effects, When the action of one drug is facilitated or increased by the other, the interaction is said to be synergistic. [2]

Priming technique is also known as auto-co-induction. It

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Manuscript Received: 15.05.2023; **Revision Accepted**: 17.07.2023;

Published Online First: 10 January, 2024.

Open Access at: https://journal.jkscience.org

Cite this article as: Kouser H, Bhadrala N, Jamwal A, Umbreen U. Comparative evaluation of standard propofol induction with propofol priming and midazolam-propofol co-induction in patients undergoing general anesthesia. JK Science 2024;26(1):7-11.

is a technique where we administer a pre-calculated dose of induction agent before administering full dose of same agent. [3] This technique, in relation to induction agents, aims at utilising the sedative and anxiolytic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction. The main objective of this technique is to reduce adverse effects and dose of induction agents such as propofol.

Propofol and midazolam is a commonly used combination for co- induction as it shows synergistic interaction for hypnosis and reflex sympathetic suppression. The reduction in the induction dose by applying "priming principle" could be attributed to the anxiolytic effect of propofol at subhypnotic doses. [4]

Our study aims to compare the effectiveness and evaluate the use of propofol and midazolam as priming (auto co-induction) and co-induction agents respectively with standard propofol induction and to find whether each of the drug midazolam or propofol is effective in reducing the induction dose of propofol (Primary outcome). The secondary outcome is to compare the hemodynamic parameters and incidence of apnoea in these groups.

Methods

The study was prospective randomized controlled study done at Postgraduate Department of Anaesthesiology, Govt Medical College, Jammu initiated after obtaining approval from ethical commitiee of the institute. 120 adult patients with ASA grade I & II, aged between 20-60 years of either gender undergoing elective general surgical, orthopaedic, ENT and gynaecological procedures under general anaesthesia were included in the trial while as patients with significant cardiovascular ,respiratory disorders, pregnancy, lactating women ,patients with known allergy to study drugs, and with drug abuse were excluded from the study. After proper informed consent, patients were randomly divided into three group (A,B and C)with 40 in each group. *Group A* patients received 0.4 mg/kg propofol injection diluted with Normal Saline to make total amount to 5 ml (priming),*Group B* patients received 0.03 mg/kg midazolam injection diluted with Normal Saline to make a total amount of 5ml (co-induction) while as Group C received 5 ml of Normal Saline.

Premedication was done with intravenous injection ondansetron (0.1mg/kg) and intravenous injection tramadol (1mg/kg). All patients were pre-oxygenated with 100% oxygen for 3 minutes. After pre-oxygenation, Group A received 0.4 mg/kg propofol injection, Group B received 0.03mg/kg midazolam and Group C received 5 ml of normal saline (control) intravenously. Two minutes after receiving the co-induction drug, the remaining propofol was administered as injection propofol 30mg I/V bolus followed by 10 mg of propofol every 10 seconds till loss of verbal response. Thereafter, succinylcholine 1.5mg/kg was given intravenously and endotracheal intubation was done with appropriate size of endotracheal tube. Subsequent relaxation was done with bolus injection of vecuronium 0.1mg/kg and anaesthesia was maintained with nitrous oxide and oxygen (60%:40%) and inhalational agent i.e. isoflurane (0.8% -1.0%). Muscle relaxation was facilitated with intermittent top-up doses of Injection vecuronium 0.02 mg/kg intravenously. Injection paracetamol 1 gram intravenous infusion was given to patients for analgesia in the intra-operative period. Total induction dose of propofol and associated baseline hemodynamic parameters like MABP, SBP, DBP, HR and SPO2 were recorded pre-induction and 1, 2, 5 and 10 minutes post-induction and thereafter at regular intervals of 10 minutes till patient was extubated. Apnoea was watched for during induction(Apnoea is defined as loss of respiratory effort for more than 20 sec or fall in SPO2 below 95%).

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Continuous variables were expressed as Mean ± SD and categorical variables were summarized as percentages. Analysis of variance (ANOVA) was employed for inter group analysis of data and for multiple comparisons, least significant difference (LSD) test was applied. Chi-square test or Fisher's exact test, whichever appropriate was used for comparison of categorical variables. Graphically the data was presented by bar and line diagrams. A P-value of less than 0.05 was considered statistically significant. All P-values were two tailed.

Results

The demographic profile of patients including age, sex and weight were statistically insignificant ($p>0.05$) in our study.

Induction dose and total dose of Propofol was least in Group B (Midazolam-Propofol group). The comparison of induction dose and total dose of propofol between three groups was stastically significant ($p<0.001$).

After induction, heart rate in all the groups decreased upto 20 minutes of induction with highest decrease in Group C and least decrease in Group B. The comparison

Table 1. Induction Dose and Total Dose of Propofol

Groups	No. of patients	Induction dose (mg/kg)	Total dose Propofol (in mg/kg)
Group A	40	1.77 ± 0.196	116.5 ± 10.51
Group B	40	1.45 ± 0.157	95.3 ± 7.16
Group C	40	2.87 ± 0.270	189.8 ± 9.47
p-value		= 0.001	=0.001

Table 2. Heart Rate at Different Time Interval (Mean ±SD).

Group	baseline	Before induction	1 min after induction	2 min after induction	5 min after induction	10 min after induction	20 min after induction
Group SP	7.13±6.98	6.05±7.07	80.83±7.8	9.18±7.82	6.05±6.13	78.85±7,26	1.38±7.02
Group MP	86.33±6.51	87.33±6,80	84.15±9.34	84.13±8.60	82.10±6.29	83.25±10.03	84.0±7.67
Group PP	87.08±6.44	87.88±6.28	76.50±6.61	74.80±6.14	71.20±6.36	74.33±5.70	78.23±4.42
P value	0.834	0.461	0.002	<0.001	<0.001	<0.001	0.006

Table 3. Mean Arterial Pressure at Different Time Interval in (Mean ± SD).

Group	Baseline MAP	Before induction	1 min after induction	2 min after induction	5 min after induction	10 min after induction	20 min after induction
Group A(SP)	98.23±9.23	98.66±9.29	100.48±6.79	89.87±5.67	88.41±6.19	90.22±5.67	92.14±6.36
Group B(MP)	97.22 ±5.98	97.27±6.12	98.81±6.49	93.47±5.20	92.63±4.57	94.12±5.89	95.09±3.49
Group C(PP)	98.21. ±6.33	7.17±6.52	04,47±5.27	2.08±4.04	2.88±4.64	72.13±4.36	82-66±2.89
P value	0.778	0.607	0.003	<0.001	<0.001	<0.001	<0.001

in change in heart rate was stastically significant (p<0.05). The comparison is statistically significant betweenGroup A vs B, Group A vs C and Group B vs C post-induction upto 30mins. However,1 minute after induction the intergroup comparisonbetween Group A vs Group B is insignificant but afterwards the comparison is significant for upto 20 minutes.

Table 4 Percentage reduction in mean arterial pressure (MAP) from baseline

Group	% reduction of MAP
Group A(SP)	10.0
Group B(MP)	4.72
Group C(PP)	26.5

Immediately after induction, significant fall in MAP was

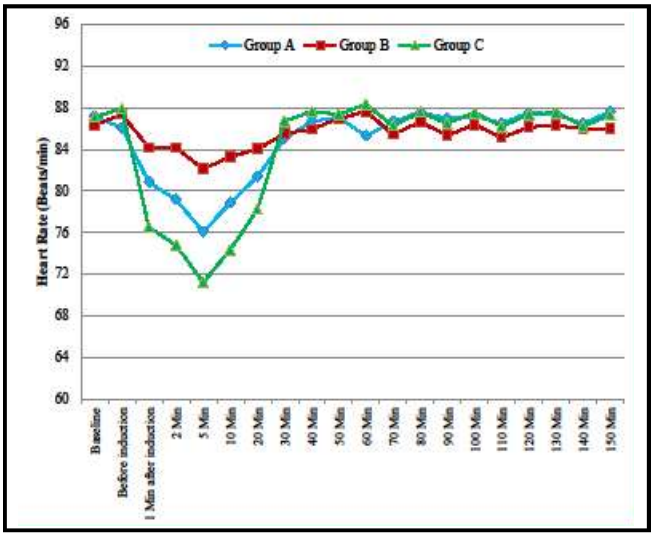

Fig 1 Heart Rate among three groups at various intervals of Time

observed in Group C (26.55%) compared to Group A (10.0%) and Group B (4.72%).

Discussion

The demographic parameters of the patients including age, sex and weight were statistically insignificant in all the three groups in our study. All the patients in three groups were comparable regarding the ASA status of the patients.

There was 38.62% and 49.79% reduction in total dose of propofol in Group A and B compared to Group C respectively. The difference in total induction dose of propofol in the study groups A and B compared to control group C was highly significant (p-value < 0.001) with Group B showing highest reduction in the total induction dose of propofol compared to Group A (p-value < 0.001). We found that co-induction with midazolam and auto co-induction with propofol reduced the dose of propofol required for induction of general anaesthesia. Dose reduction following midazolam is probably due to synergistic action between the two drugs. [4] Synergism has been reported between agents with known functional link in central nervous system viz. midazolam and propofol acting on a common respective site, the GABA receptors**.** Anderson L *et al.,*[5] proposed a pharmacokinetic theory that part of the mechanism of action of co-induction drugs is to reduce anxiety and its associated sympathetic response. When administered before induction, this mechanism reduces cardiac output which helps in preventing rapid distribution of propofol. In their study the dose of propofol required to induce anaesthesia was significantly less in patients in the midazolam co-induction group (1.71 mg/kg) and the propofol priming group (1.87 mg./kg) when compared to the control group (2.38 mg/kg). Similarly in a study done by Win NN *et al.,*[6] they showed that the total dose of propofol was significantly reduced in midazolam-propofol group compared to standard propofol group. In another study done by Mallikarjuna J *et al*.[7], there was statistically significant reduction in total dose of propofol in Group PP and Group MP compared to Group SP with highest reduction in mean induction dose of propofol in Group MP. In a study done by Pathak [8] *et al* ,they found that dose of propfol was significantly lesser in propofol infusion plus midazolam with better hemodynamic stability

In our study there was statistically significant decrease in mean heart rate from 1 minute upto 20 minutes post induction in all the three groups and heart rate was comparable at baseline. The percentage reduction in Group A, B and C was 12.71%, 4.89% and 18.23%

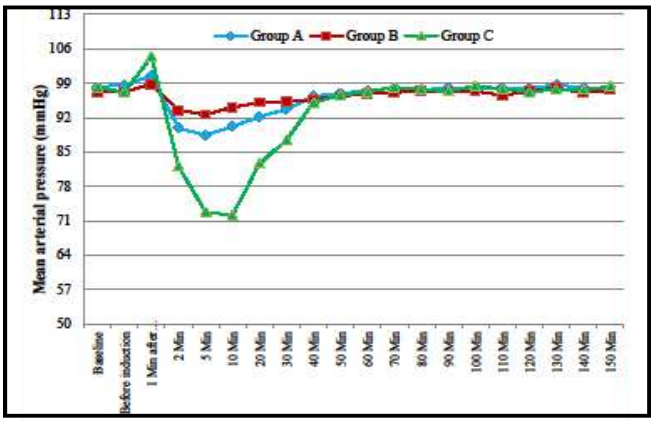

Fig.2 MAP (mm/HG) among three groups at various interval of time

respectively . The change in heart rate between the three groups was statistically significant with Group B showing least fall in heart rate. . Heart rate reduction was highest in control group (Group C). This reduction in heart rate can be attributed to vagotonic properties of propofol. In the study done by Amatya A *et al.*[9] they noticed significant reduction in heart rate from 1 to 5 minutes post-induction in propofol group, midazolam group and normal saline group.In contrast to our study, the study done by Dhanapalan SS *et al.,* [10] showed increase in heart rate which was significantly higher in control group at 1 and 3minutes after induction as compared to propofol priming group.

In our study there was statistically significant fall in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) from 1-30 minutes post–induction. The percentage fall in SBP was least in Group B (4.12%) as compared to Group A (8.85%) and Group C (24.5%), with Group C showing highest fall in SBP. The changes in systolic BP between Group A vs B , Group B vs C was statistically significant (p value < 0.05).

In our study, immediately after induction, significant fall in MAP was observed in Group C (26.55%) compared to Group A (10.0%) and Group B (4.72%) . The lesser fall in Group A & Group B was because of reduction in total induction dose of propofol after co-induction. Fall in MAP was dose dependent in Group B, the small but statistically significant fall in mean arterial pressure at post-induction period may be due to amnesic, anxiolytic and synergistic action of midazolam with propofol. These factors reduce the total dose of propofol. Lower the dose of propofol, lesser will be the fall in MAP. .In the study by Lim YS *et al.,*[11] it was found that as compared with

Group P, the decrease of MBP was significantly less in Group MP before intubation, immediately after intubation and 3 minutes after intubation. The results of this study are consistent with our study. Our study is also comparable to study done by Amatya A *et al.,*[8]. In their study there was highest fall in SBP, DBP and MAP in standard propofol group and Group M (midazolam group) showing least fall. Our results also match with the results of study done by Khandelwal S *et al.,*[12] in which they found a decrease in systolic blood pressure in all the three study groups with minimum decrease in midazolam-propofol group.

In our study we compared the incidence of apnoea during induction. We found that the incidence of apnoea was higher in Group C (20%) compared to Group B (7.5%) and Group A (12.5%). However, overall there was no statistically significant difference in apnoea between the three groups. Propofol produces dose dependent depression of ventilation with apnoea occurring in 25 to 35 % of patients after induction of anesthesia with propofol. In the study done by Mallikarjuna *et al.*[7], Standard propofol group showed highest incidence (16%) of apnoea compared to midazolam–propofol (8%) and propofol-propofol group (12%). However, the difference was not statistically significant in the study. The findings also match with results of Hui TW *et al.,*[13] and Anil K *et al.,* [14] who respectively found that propofol pre dosing resulted in lesser incidence of apnoea during induction of propofol.

Conclusion

From the present study we concluded that propofol priming and midazolam-propofol co-induction significantly decreases the average induction dose of propofol with better hemodynamic stability and least adverse effects. However, the greater decrease in induction dose of propofol and better hemodynamics were seen with the midazolam- propofol co-induction.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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