A COMPARATIVE STUDY OF SMALL DOSE OF KETAMINE, MIDAZOLAM AND PROPOFOL AS COINDUCTION AGENT TO PROPOFOL

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ABSTRACT

BACKGROUND

The technique of "coinduction", i.e. use of a small dose of sedative agent or another anaesthetic agent reduces the dose requirement as well as adverse effects of the main inducing agent. Ketamine, midazolam and propofol have been used as coinduction agents with propofol.

MATERIALS AND METHODS

This prospective, randomised clinical study compared to three methods of coinduction. One group received ketamine, one group received midazolam and one group received propofol as coinducing agent with propofol.

RESULTS

The study showed that the group receiving ketamine as coinduction agent required least amount of propofol for induction and was also associated with lesser side effects.

CONCLUSION

Use of ketamine as coinduction agent leads to maximum reduction of induction dose of propofol and also lesser side effects as compared to propofol and midazolam.

KEYWORDS

Coinduction, Propofol, Midazolam, Ketamine.

HOW TO CITE THIS ARTICLE: Kalita A, Ahmed ALM. A comparative study of small dose of ketamine, midazolam and propofol as coinduction agent to propofol. J. Evid. Based Med. Healthc. 2017; 4(64), 3820-3825. DOI: 10.18410/jebmh/2017/763

BACKGROUND

Propofol is the most frequently used IV anaesthetic agent used today with a desirable anaesthetic profile. It provides faster onset of action, antiemesis, rapid recovery with attenuation of pharyngeal, laryngeal and tracheal reflexes and also adequate depth of anaesthesia during intubation. But, the major disadvantages of propofol are impaired cardiovascular and respiratory function, which may put the patient at higher risk of bradycardia, hypotension and apnoea. Propofol is insoluble in water and was initially prepared with cremophor EL. But, for the anaphylactoid reactions associated with cremophor EL, this drug was later formulated as an emulsion. The induction dose of propofol (2 to 2.5 mg/kg in healthy adults) produces unconsciousness depending on concomitant medications, patient's age and physical status of the patient and the extent of surgical stimulation. Its onset is within 15 to 45 seconds and duration of action is for 5 to 10 minutes.

Financial or Other, Competing Interest: None.
Submission 13-07-2017, Peer Review 20-07-2017,
Acceptance 03-08-2017, Published 08-08-2017.
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DOI: 10.18410/jebmh/2017/763

But, the major disadvantage of propofol induction are impaired cardiovascular and respiratory function, which may put the patients at a higher risk of bradycardia, hypotension and apnoea. A decrease of 26-28% of Systolic Blood Pressure (SBP), 19% of Diastolic Blood Pressure (DBP) and 11% of Mean Arterial Pressure (MAP) with changes in stroke volume and cardiac output is observed when anaesthesia is induced with 2 mg/kg of propofol.[1,2] The mechanism of hypotension has been attributed to a decrease in sympathetic activity,[3] myocardial depression[4,5,6] and direct vasodilation.[4,5,7] The hypotensive effects of propofol are generally related to the dose and rate of administration of propofol.[8,9]

The technique of coinduction is to administer a subanaesthetic dose of another inducing or sedative agent, so as to reduce the dose of the primary inducing agent.[10,11] The main objective of this is to improve the ratio of desired versus adverse effects and also to reduce the cost of expensive drugs such as propofol. Several group of drugs like benzodiazepines and ketamine.[12,8] Opioids like fentanyl, thiopentone and even propofol itself in small doses have been tried as coinducing agents with propofol.

Midazolam has been the most commonly used coinducing agent with propofol.[9,13] It is a benzodiazepine, which increases the GABA mediated chloride ion conduction and is used for premedication, sedation, induction and coinduction of anaesthesia.

Ketamine has also been used as a coinducing agent. The advantages of ketamine include better haemodynamic stability.[12,8]

Also, in recent studies, it has shown that if a small dose of propofol was given prior to induction dose of propofol itself (called auto-coinduction), there is considerable reduction in the dose of propofol required for induction along with less haemodynamic effects.[14]

MATERIALS AND METHODS

The present study was conducted in a tertiary care institute from July 2015 to June 2016 after getting approval from the institutional ethical committee. Written informed consent was taken from each patient after explaining the study procedure to them in their own language.

A total of 150 patients undergoing various general surgical, urologic, orthopaedic and gynaecological procedures under general anaesthesia were selected and were divided randomly into 3 groups consisting of 50 patients in each group. Patients between 20 to 50 years of age of ASA grade I and II were included in the study. Exclusion criteria were patient refusal, allergy to any drugs, patients with ASA grade III or higher, history of seizure, hypertension, neurological or endocrine disorders.

The study was a prospective, randomised clinical trial. The selected patients were randomly divided into three main groups- group KP received ketamine 0.3 mg/kg IV as coinduction agent, group MP received midazolam 0.03 mg/kg as coinduction agent and group PP received propofol 0.4 mg/kg as the coinducing agent. Propofol was used as the primary inducing agent in all the three.

The patients were visited in the ward for preanaesthetic checkup in the evening before the day of surgery. A detailed history was taken and a thorough clinical examination was done. The patients were explained about the study procedure and an informed consent was taken. Each patient received bowel cleansing procedure and tablet alprazolam. 5 mg the night before surgery. Patients were kept nil orally until the surgery the next day. After positioning the patient in the OT table, the patient will be cannulated with an 18 G peripheral cannula and a lactated Ringer's drip connected, followed by attachment of the ECG leads, noninvasive blood pressure cuff and the pulse oximetry probe. Baseline SBP, DBP, MAP and HR will be noted. The patients in all the groups will receive Inj. Ondansetron 4 mg slow IV, Inj. Tramadol 1.5 mg/kg body weight IV, Inj. Glycopyrrolate 0.2 mg IV and Inj. Ketorolac hydrochloride. 5 mg/kg body weight IV as premedication 10 minutes before induction.

Technique of Anaesthesia- First, the patients were preoxygenated with 100% oxygen for 3 minutes and then the coinducing agent was given, which was 0.3 mg/kg ketamine (Group KP), 0.3 mg/kg midazolam (Group MP) and 0.4 mg/kg propofol (Group PP).

The coinducing agent was prepared in a 10-mL syringe and the amount was made to 10 mL. 2 minutes after the coinducing agent, each patient received 2 mL of lignocaine followed by propofol at the rate of 30 mg every 10 seconds till the loss of verbal commands.

Subsequent relaxation and intubation was achieved with Inj. Suxamethonium 1.5 mg/kg IV and anaesthesia was maintained with O2 + N2O (33/66), Inj. Atracurium in top-up dose as muscle relaxant and isoflurane. Patients were reversed at the end of surgery with neostigmine and glycopyrrolate.

The following parameters were recorded-

1. The total dose of propofol needed for induction.
2. Heart rate and mean arterial pressure-
    a. Baseline.
    b. 1 minute after coinducing agent.
    c. 1 minute after inducing agent.
    d. Then, every 5 minutes till 20 minutes after inducing agent.

The data was recorded on predesigned and pretested proforma was tabulated and the master chart was prepared. The statistical analysis was done using the SPSS and ANOVA was applied between the three groups. Further post-hoc analysis was done in the parameters, which were statistically significant in ANOVA by using the Bonferroni t-test.

RESULTS AND OBSERVATIONS

Demographic data such as age, weight, gender and ASA grading were comparable among the three groups.

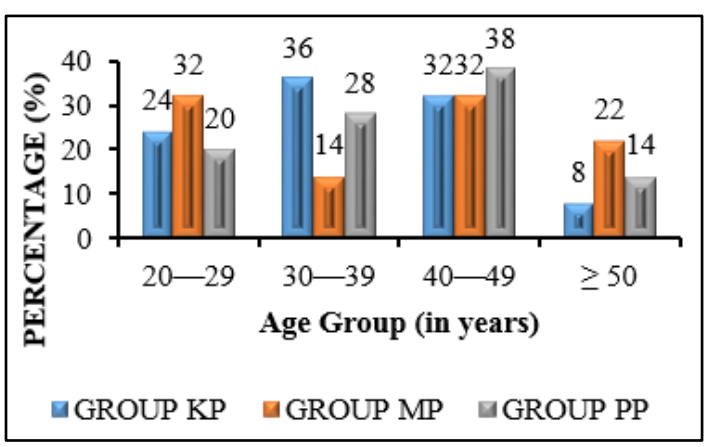

Figure 1.1. Age Distribution

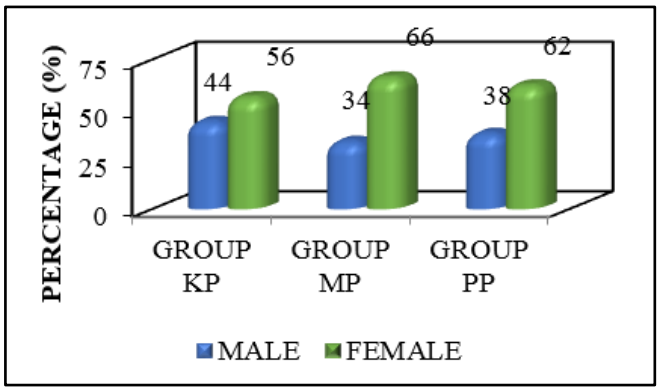

Figure 1.2. Sex Distribution

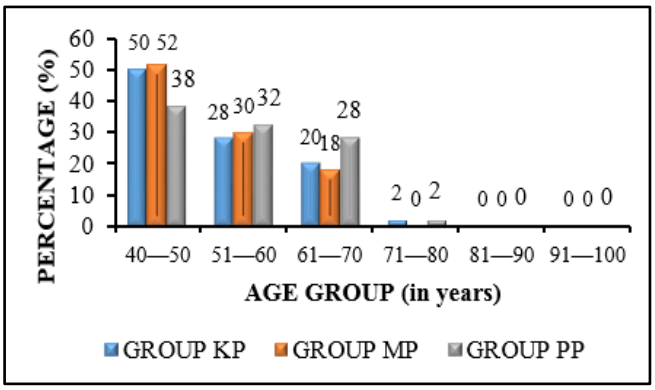

Figure 1.3. Weight Distribution

The mean induction dose of propofol in the ketamine group was 1.43 mg/kg, which was significantly lesser than that of the midazolam group (1.65 mg/kg) and the propofol group (1.70 mg/kg). Further the induction dose of midazolam was significantly higher than that of propofol.

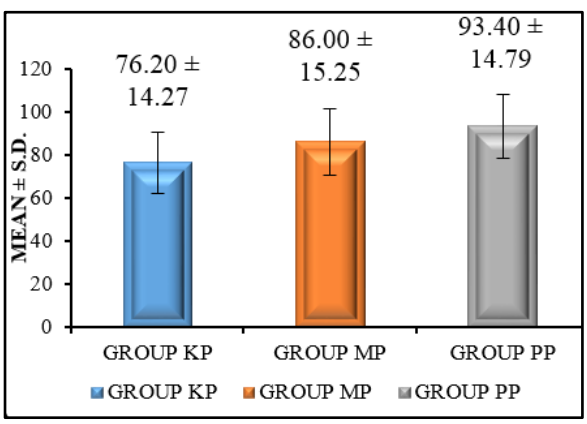

Figure 2. Induction Dose

At 1 minute after coinduction, there was a rise of SBP, DBP and MAP in the KP group, whereas in the other two groups MP and PP, there was a fall in SBP, DBP and MAP. At 1 minute after induction, there was a fall in SBP, DBP and MAP in all the three groups. The fall in KP group was significantly lesser than that of the groups MP and PP. Again, at 5 minutes after intubation, the SBP, DBP and MAP in the KP group was significantly higher than that of groups MP and PP.

At 1 minute after induction, the fall in heart rate from baseline was significantly lesser in the Ketamine group as compared with the midazolam and propofol group. However, the difference between the HR between the midazolam and propofol group was not statistically significant. Again, at 5 minutes after intubation, mean HR in the KP group was significantly higher than that of the groups MP and PP, whereas there was no significant difference between groups MP and PP.

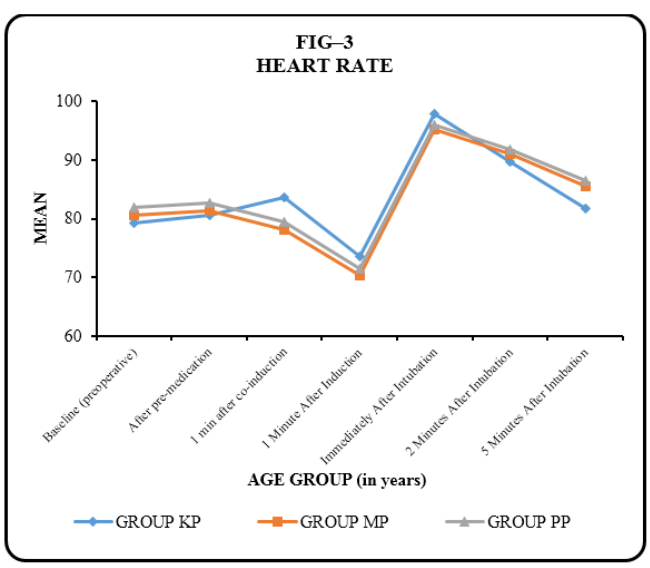

Figure 3. Heart Rate

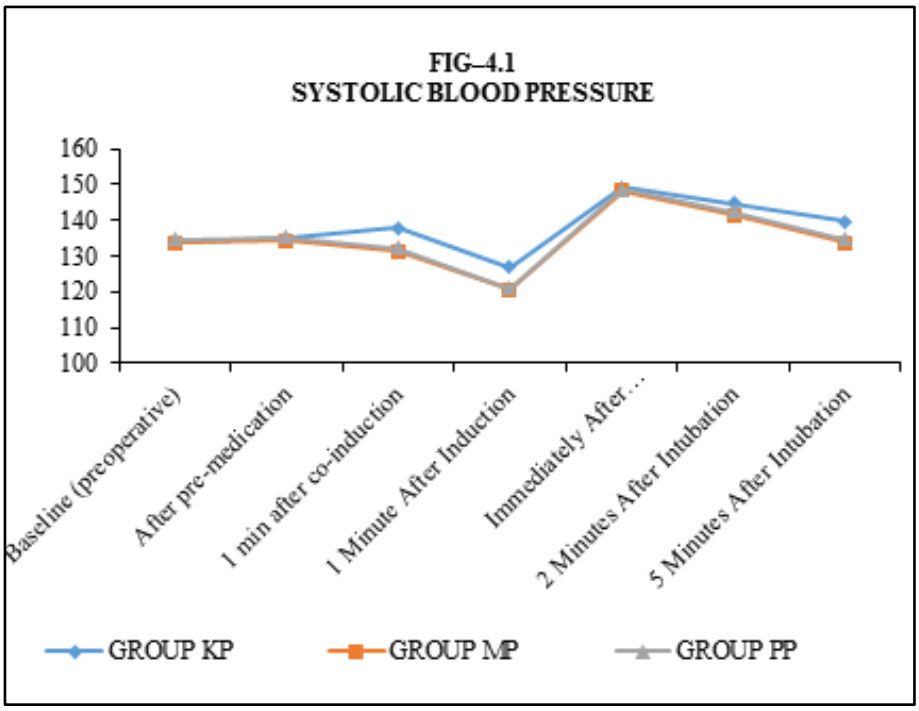

Figure 4.1. Systolic Blood Pressure

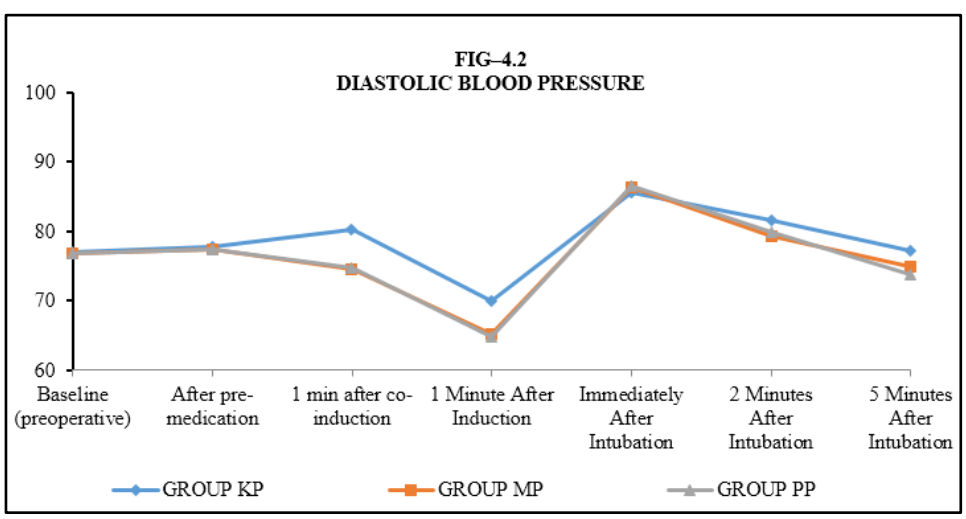

Figure 4.2. Diastolic Blood Pressure

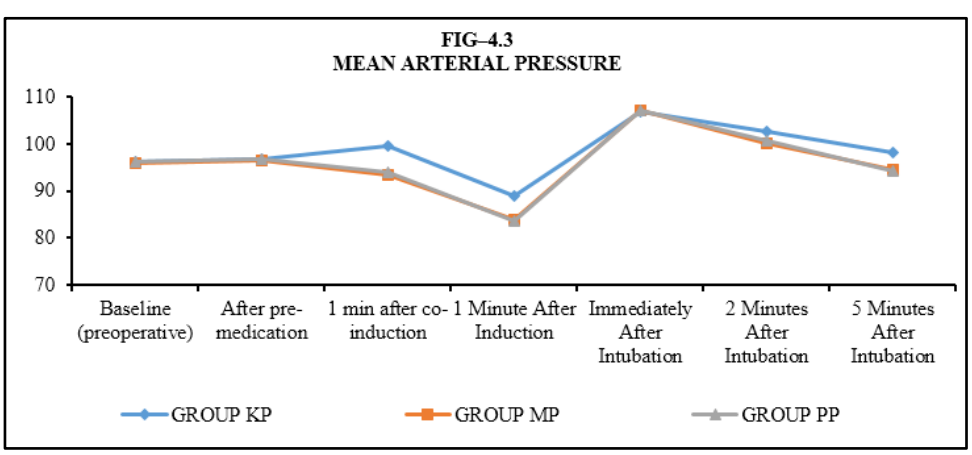

Figure 4.3. Mean Arterial Pressure

Incidence of apnoea after induction was lesser in the KP group (8%) as compared to the MP (16%) and PP (14%) group.

DISCUSSION

The aim of the study is to compare the dose reduction of propofol when small doses of midazolam, ketamine and propofol are used as coinducing agents with propofol and to compare the associated haemodynamic changes.

150 adult patients of ASA grade I and II were allocated randomly by envelope method using random number tables into 3 groups of 50 each- Group KP- ketamine-propofol group; Group MP- Midazolam-propofol; Group PP -propofol-propofol group.

The mean induction dose of propofol in the ketamine group (KP) was 76.20 mg (1.43 mg/kg), that in the midazolam (MP) group, it was 86.00 mg (1.65 mg/kg), and that in the propofol group (PP), it was (1.70 mg/kg). The required induction dose was least in the KP group and there was statistically significant difference in the doses between the groups KP and MP and also between the groups KP and PP. Further the induction dose in the midazolam (MP) group was higher than the propofol (PP) group and the difference was statistically significant.

Similar results were observed by Uma Srivastava et al (2006)[15] who compared the induction dose of propofol with propofol, ketamine and midazolam. Neelesh Nema et al (2014)[16] also compared the induction doses of propofol with use of ketamine, midazolam and propofol as coinducing agents. Both these studies found that the required induction dose is least with propofol.

Gojendra Kumar et al (2013)[17] in their comparison between midazolam, thiopentone and ketamine as coinduction agents with propofol found the propofol dose requirement to be least with ketamine. R Kataria et al (2010) compared the mean induction doses of propofol with midazolam and propofol auto coinduction with a control group. They found the mean induction dose to be least in the midazolam group, lesser in the propofol group as compared to the control group and the difference was calculated to be statistically significant.

Also, we observed that the heart rate of the patients in the group KP were significantly higher than that of MP and PP at 1 min. after coinduction, 1 min. after induction and 5 mins. after intubation. In the readings immediately after intubation and 2 mins. after intubation, the HR was higher in the KP group than the MP and PP group, but the difference was not statistically significant, whereas between the groups MP and PP heart rate was higher in PP group at 1 min. after coinduction, 1 min. after induction, immediately after intubation and at 2 mins. and 5 mins. after intubation, but the difference was not statistically significant at any of the intervals.

At 1 min. after coinduction, we observed a mild increase in SBP, DBP and MAP from the baseline value in the group KP, whereas in the groups MP and PP, there was a slight fall in the blood pressures. The values of SBP, DBP and MAP of group KP was significantly higher than that of MP and PP. However, the difference in BPs between the groups MP and PP were not statistically significant. There was a decrease in SBP, DBP and MAP from baseline value in all the 3 groups, at 1 min. after induction. The reduction in systolic blood pressure was 5.40% in the KP group, 9.80% in the MP group and 10.04% in the PP group. The fall in diastolic blood pressure was 9.15% in the KP group, 15.01% in the MP group and 15.77% in the PP group. Similarly, the fall in mean blood pressure was 7.39% in the KP group, 12.60% in the MP group and 13.09% in the PP group. The difference in SBP, DBP and MAP between the group KP and that of groups MP and PP at 1 min. after induction was statistically significant. Whereas, the difference between SBP, DBP and MAP between groups MP and PP was not statistically significant. Thus, we observed a significantly lesser fall in the blood pressure (SBP, DBP, MAP) in group KP as compared to groups MP and PP confirming that the fall in arterial blood pressure was dose-dependent.

Immediately after intubation, the blood pressures (SBP, DBP, MAP) were at a higher range in all the three groups than when compared to 1 min. after induction. However, the difference between the BP among the three groups were not statistically significant.

Again, at two minutes after intubation, the SBP, DBP and MAP in all the three groups were slightly higher in comparison to the baseline values, but there were no significant difference between the SBP, DBP and MAP among the three groups.

Similarly, at 5 mins. after intubation, the SBP, DBP and MAP of the group KP was marginally higher when compared with the baseline values, whereas in the groups MP and PP, the SBP, DBP and MAP were marginally lower as compared with baseline values. The SBP, DBP and MAP of the group KP at 5 mins. after intubation was significantly higher than that of MP and PP. However, the difference in the corresponding values between MP and PP was not statistically significant.

Induction with propofol is accompanied by a few undesirable side effects like pain on injection, apnoea and hypotension. In the present study, 10% of the patients in group KP, 16% patients in group MP and 16% patients in group PP complained of pain on injection. The difference in incidence in pain on propofol injection between the three groups was not statistically significant.

CONCLUSION

In conclusion, our study showed that ketamine when used as coinducing agent causes minimum dose requirement of propofol for induction as compared to midazolam and propofol auto coinduction. Also, ketamine is associated with lesser fall of heart rate and arterial blood pressure after induction than with midazolam and propofol auto-coinduction, whereas on comparison between midazolam and propofol, induction dose of propofol was found to be significantly lesser with midazolam than with propofol auto-coinduction, while the fall in heart rate and arterial blood pressure was similar between the two groups. Also, the incidence of overall adverse events was comparable among the three groups.

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