A Comparative Study of Small Dose of Ketamine and Midazolam as Co-Induction Agents to Propofol in Patients Undergoing Elective Surgeries under General Anaesthesia

Disha Ubeja[1], Ravishankar R.B.[2]

[1, 2] Department of Anaesthesiology and Critical Care, JJM Medical College, Davangere, Karnataka, India.

ABSTRACT

BACKGROUND

Intravenous anaesthesia is an integral part of modern anaesthesia. But till date there is no single intravenous agent which fulfils all the characteristics of an ideal anaesthetic agent. The technique of co-induction is to administer a subanaesthetic dose of another inducing or sedative agent, so as to reduce the dose of primary agent. Propofol in the most frequently used IV anaesthetic agent used today, providing faster onset of action, antiemesis, rapid recovery with attenuation of pharyngeal, laryngeal and tracheal reflexes. The major disadvantages of propofol induction are impaired cardiovascular and respiratory function, which may put the patient at a higher risk of bradycardia, hypotension and apnoea.

METHODS

150 patients of either sex in the age group of 18 to 65 years, undergoing elective surgeries were randomly selected and informed consents were taken. The study population was divided into three groups with 50 patients in each group. Group KP- 0.4 mg/Kg ketamine; Group MP- 0.03 mg/Kg midazolam and Group C- 10 mL NS.

RESULTS

Requirement of induction dose was reduced in both the groups and the induction dose was the least in group KP. Changes in haemodynamic parameters ere greater in group c and group MP as compared to group KP.

CONCLUSIONS

Co-induction with ketamine provides better hemodynamic stability and lesser induction dose of propofol as compared to midazolam. Therefore, ketamine is preferred as a co-induction agent to propofol.

KEYWORDS

Propofol, Ketamine, Midazolam

Corresponding Author:
Dr. Disha Ubeja,
Near Santosh Lodge,
Juni Line, Bilaspur- 495001,
Chhattisgarh, India.
E-mail: dishaubeja@gmail.com

DOI: 10.18410/jebmh/2020/528

How to Cite This Article:
Ubeja D, Ravishankar RB. A comparative study of small dose of ketamine and midazolam as co-induction agent to propofol in patients undergoing elective surgeries under general anaesthesia. J Evid Based Med Healthc 2020; 7(44), 2557-2561. DOI: 10.18410/jebmh/2020/528

Submission 20-04-2020,
Peer Review 28-04-2020,
Acceptance 28-06-2020,
Published 02-11-2020.

BACKGROUND

General anaesthesia is an important component of modern medicine. General anaesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. General anaesthesia is associated with various effects on the respiratory and cardiovascular system, which includes loss of airway patency, loss of protective airway reflexes, hypoventilation or apnoea, hypotension or bradycardia. There are several pharmacologic techniques, used for the induction of general anaesthesia. Induction can be achieved either by administration of a intravenous agent or inhaled induction with volatile anaesthetic agent. The commonly used approach in adults is standard IV induction, followed by administration of a neuromuscular blocking drug. Inhalational technique is mostly used in paediatric patients to provide a painless, needle free experience for the child. The induction period begins with the administration of an intravenous agent.

An ideal induction agent should have a rapid onset of action, rapid recovery, and should have minimal cardiovascular and respiratory impairment. But till date there is no single intravenous agent which fulfils all the characteristics of an ideal anaesthetic agent. The term co-induction of anaesthesia has been applied to the use of two or more drugs to induce anaesthesia. The term was introduced in 1986 to describe the unplanned induction of anaesthesia by non-anaesthetically trained personnel practicing sedation. Currently, planned co-induction of anaesthesia is practiced by anaesthetists exploiting drug interactions, particularly synergism.[1] It can produce an improvement in all phases of anaesthesia, including induction, maintenance and recovery.

The technique of co-induction is to administer a subanaesthetic dose of another inducing or sedative agent, so as to reduce the dose of primary inducing agent. 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.[2]

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 disadvantage of propofol induction is that it causes a dose-dependent decrease in cardiac output and systemic vascular resistance and produces moderate respiratory depression, which may put the patient at a higher risk of bradycardia, hypotension and apnoea.[1,2]

Midazolam is a benzodiazepine, which increases the GABA mediated chloride ion conduction and is used for premedication, sedation, induction and co-induction of anaesthesia.[2]

Ketamine is a phencyclidine derivative that acts primarily, but not entirely, as an antagonist of the N-methyl-D-aspartate receptor. It produces dissociative anaesthesia. In contrast to other anaesthetic agents, ketamine increases arterial blood pressure, heart rate and cardiac output. Ketamine has minimal effect on respiration and tends to preserve autonomic reflexes. The incidence of its psychomimetic effects can be reduced by co administration of benzodiazepine, barbiturate or propofol. Using ketamine in subanaesthetic doses, the adverse effects are not seen, but at the same time it acts as an analgesic and co-induction agent.

The present study is being undertaken to compare the efficacy of small doses of ketamine (0.4 mg/Kg) and midazolam (0.03 mg/Kg) as co-induction agents to propofol with respect to hemodynamic changes and induction dose of propofol.

We wanted to evaluate and compare

1. Dose of propofol required for induction.
2. Blood pressure variability during induction.
3. Heart rate variability during induction.
4. Side effects if any.

METHODS

A randomized prospective study entitled 'A Comparative Study Of Small Dose Of Ketamine And Midazolam As Co-induction Agents to Propofol In Patients Undergoing Elective Surgeries Under General Anaesthesia' was conducted on 150 patients aged between 16-65 years at Chigateri General Hospital and Bapuji Hospital attached to J.J.M. Medical College, Davangere during the academic year from October 2017 to September 2019.

In this randomized, clinical study, we studied 150 ASA Grade I and II patients between the ages of 16-65 years undergoing elective surgeries under general anaesthesia. Approval was taken from Institutional ethics review committee and written informed consent was taken from all the patients after explaining the study to them. Result values were recorded using a pre-set proforma.

Based on the inclusion and exclusion criteria, 150 patients of ASA Grade I and II, posted for elective surgeries under general anaesthesia were selected and randomly divided into three equal groups of 50 each.

- Group KP received 0.4 mg/Kg ketamine.
- Group MP received 0.03 mg/Kg midazolam.
- Group C received 10 ml normal saline.

Inclusion Criteria

- Age-18-65 years
- Both sexes
- ASA I-II

Exclusion Criteria

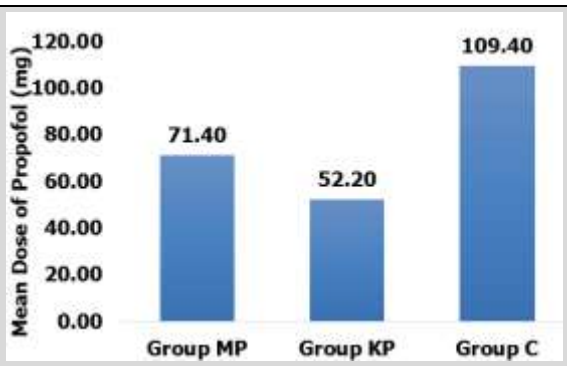
- Patient refusal
- Previous history of allergy to ketamine or midazolam

- History of seizure
- Hypertension
- Pregnant or lactating mother
- Neurological or endocrine disorder

RESULTS

			Mean	SD	F Value	P Value
Dose of propofol (mg)	Group MP	50	71.40	8.332	521.562	0.000
	Group KP	50	52.20	6.481		
	Group C	50	109.40	11.502		

Table 1. Dose of Propofol Needed for Induction



Graph 1. Dose of Propofol Needed for Induction

Heart Rate	Group MP		Group KP		Group C		F	P
	Mean	SD	Mean	SD	Mean	SD	Value	Value
Baseline	86.42	13.68	87.72	13.04	82.78	7.28	2.397	0.095
1 Min after Co-Induction	81.02	13.64	96.88	13.17	83.22	7.19	26.929	<0.05
1 Min after Induction	76.3	13.0	81.7	12.4	67.8	6.7	19.944	<0.05
2 Mins after Induction	81.0	12.9	92.9	13.3	68.5	6.7	57.497	<0.05
5 Mins after Induction	86.1	12.7	91.4	12.7	68.7	6.7	57.425	<0.05
10 Mins after Induction	79.9	12.0	80.7	12.4	68.7	6.7	19.372	<0.05
15 Mins after Induction	76.2	12.0	83.8	12.8	68.7	6.7	24.208	<0.05
20 Mins after Induction	73.3	12.2	83.7	13.0	68.7	6.7	24.306	<0.05

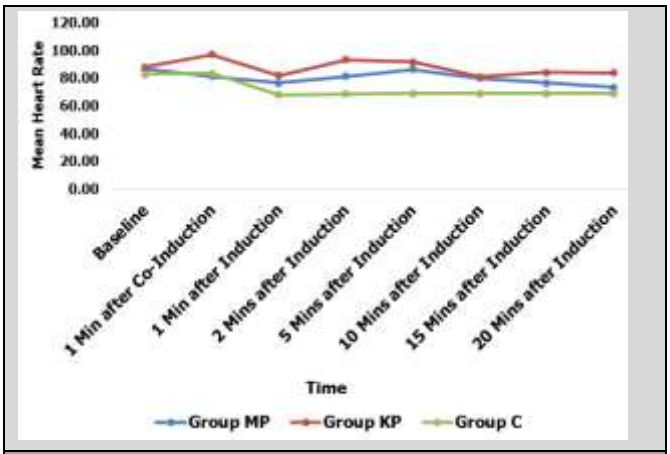
Table 2. Comparison of Heart Rate (Beats/Min.) in Study Groups

SBP	Group MP		Group KP		Group C		F	P
	Mean	SD	Mean	SD	Mean	SD	Value	Value
Baseline	127.66	9.03	119.78	10.44	124.96	7.13	9.972	<0.05
1 Min after Co-Induction	121.20	7.99	124.80	10.24	124.84	7.13	2.986	0.054
1 Min after Induction	115.00	7.84	114.70	10.06	100.58	6.68	49.127	<0.05
2 Mins after Induction	121.12	6.68	120.08	9.99	100.58	6.68	106.245	<0.05
5 Mins after Induction	125.80	6.67	120.98	9.93	111.32	6.89	42.805	<0.05
10 Mins after Induction	118.84	6.98	113.72	9.77	105.28	6.88	36.752	<0.05
15 Mins after Induction	115.40	7.37	114.26	9.30	105.28	6.88	24.516	<0.05
20 Mins after Induction	114.26	7.50	114.80	9.07	105.28	6.88	23.075	<0.05

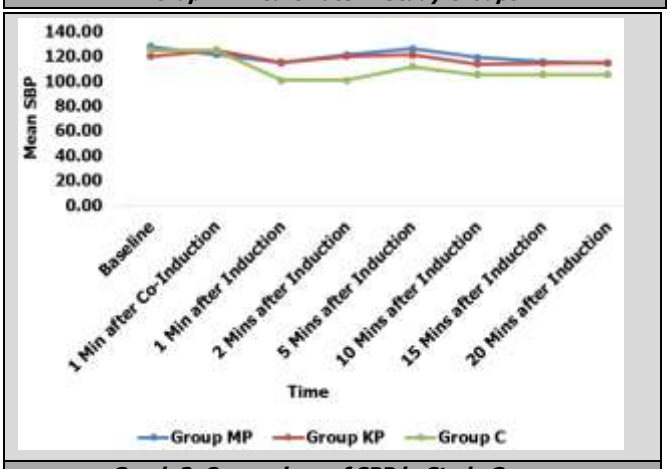
Table 3. Comparison of SBP in Study Groups

DBP	Group MP		Group KP		Group C		F	P
	Mean	SD	Mean	SD	Mean	SD	Value	Value
Baseline	80.16	7.81	77.80	7.05	77.58	4.76	2.302	0.104
1 Min after Co-Induction	74.68	7.42	81.84	6.90	77.58	4.76	15.527	<0.05
1 Min after Induction	69.48	7.11	71.02	6.56	52.88	4.69	131.216	<0.05
2 Mins after Induction	74.24	6.89	76.16	6.61	52.88	4.69	221.333	<0.05
5 Mins after Induction	78.48	6.51	76.18	6.54	63.56	4.76	89.821	<0.05
10 Mins after Induction	71.92	6.63	74.26	6.92	57.60	4.73	106.898	<0.05
15 Mins after Induction	69.68	6.84	73.68	6.87	57.60	4.73	90.373	<0.05
20 Mins after Induction	69.20	6.94	73.14	6.96	57.60	4.73	82.249	<0.05

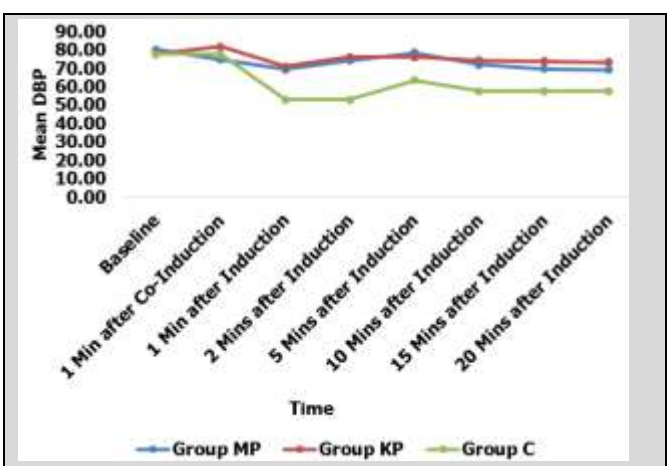
Table 4. Comparison of DBP in Study Groups



Graph 2. Heart Rate in Study Groups



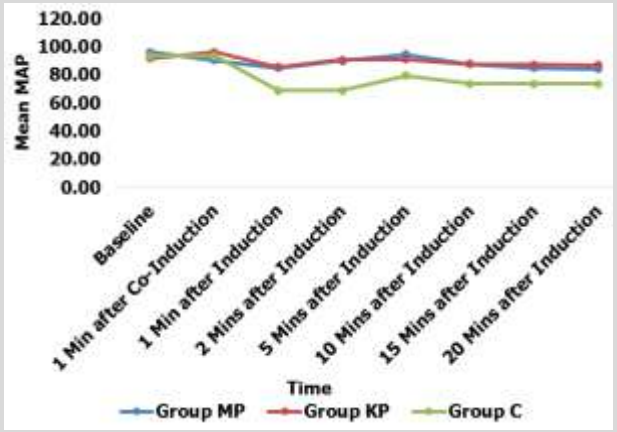
Graph 3. Comparison of SBP in Study Groups



Graph 4. Comparison of DBP in Study Groups

MAP	Group MP		Group KP		Group C		F	P
	Mean	SD	Mean	SD	Mean	SD	Value	Value
Baseline	96.02	6.84	91.78	6.78	93.38	4.57	6.050	0.003
1 Min after Co-Induction	90.19	6.36	96.16	6.63	93.33	4.54	12.751	<0.05
1 Min after Induction	84.66	6.27	85.62	6.39	68.76	4.34	135.881	<0.05
2 Mins after Induction	89.86	5.71	90.78	6.23	68.76	4.34	258.025	<0.05
5 Mins after Induction	94.30	5.32	91.06	6.17	79.48	4.45	105.634	<0.05
10 Mins after Induction	87.56	5.41	87.42	6.22	73.48	4.45	111.713	<0.05
15 Mins after Induction	84.96	5.59	87.22	6.13	73.48	4.45	91.780	<0.05
20 Mins after Induction	84.22	5.69	86.96	6.25	73.48	4.45	83.410	<0.05

Table 5. Comparison of MAP in Study Groups



Graph 5. Comparison of MAP in Study Groups

DISCUSSION

The development of intravenous agents has been an important aspect of anaesthetic management. Rapid emergence from anaesthesia and post-operative recovery of cognitive function as well as hemodynamic stability is an important requirement of modern anaesthesia.[3] Co-induction is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia. This technique aims at utilizing the sedative, anxiolytic, amnesic and analgesic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction.[4] Propofol, the most commonly used IV induction agent because of its fast onset and quick recovery but the major disadvantage with propofol is unstable haemodynamics. Propofol causes a greater drop is heart rate and arterial pressures.[5] The rationale behind co-induction is to achieve more specific responses while minimizing the side effects. The objection of this technique is to improve the ratio of desired versus adverse effects.[6] This study is undertaken to compare and assess the efficacy of ketamine and midazolam as co-induction agents to propofol with respect to induction dose of propofol and hemodynamic stability In our study 150 patients of ASA grade I and II, belonging to group between 16-65 years, of which majority were in between 16-25 years and 26-35 years, undergoing routine surgical procedures under general anaesthesia were selected and randomly divided into three groups as Group MP- midazolam propofol, Group KP- ketamine propofol and Group C- control group. The three groups were comparable in terms of sex distribution, mean age and ASA status.

Dose of Propofol Needed for Induction

In our study, mean dose of propofol in Group MP was 71.4± 8.3 mg. In group KP mean dose was 52.2±6.4 mg and in group C it was 109.4±11.5 mg. Statistical analysis was done using ANOVA test showed that the difference between three groups was statistically significant with p value <0.05. Neelesh Nema et al[7] in their study " A comparative study of small dose ketamine, midazolam and propofol as co-induction agents to propofol" found the dose of propofol in Group MP was 81.58±6.89 mg, in group KP was 71.5±6.26 mg and in Group SP was 157.22±13.39 mg

Srivastava Uma et al[8] in their study "Small dose propofol or ketamine as an alternative to midazolam co-induction to propofol" concluded the mean dose of propofol varied significantly, being highest in control group and lowest in ketamine group and was statistically significant.

Heart Rate

In our study, percentage fall in heart rate from baseline in group MP was 15.29%, group KP was 4.67% and in group C was 17.07% with p value <0.05 and was statistically significant. Our results were in accordance with the study conducted by Neelesh Nema et al which showed that the percentage fall in heart from baseline was 14.9% in midazolam propofol group, 3.38% in ketamine propofol group and 15.17% in control group. Raj Kumar et al in their study "Co-induction effects of midazolam, thiopentone and ketamine with propofol in general anaesthesia" concluded that HR stability was best maintained with ketamine.

Systolic Blood Pressure

In our study, systolic blood pressure was found to decrease in all the three study groups following induction. After co-induction the systolic blood pressure in Group KP is increased initially. In group KP change in systolic blood pressure was least in comparison to other two groups and it was statistically significant. (p<0.0.5) In our study, percentage fall in SBP from baseline in group MP was 10.53%, in group KP was 4.08% and in group C was 15.78% with p value <0.05 and was statistically significant. Abhimanyu Kalita et al in their study "A comparative study of small dose ketamine, midazolam and propofol as co-induction agent to propofol" found that the reduction in systolic blood pressure was 5.40% in group KP, 9.80% in the MP group and 10.04% in the PP group.

Diastolic Blood Pressure

In our study, diastolic blood pressure was found to decrease in all the three study groups following induction. After co-induction the diastolic blood pressure in Group KP is increased initially. In group KP change in diastolic blood pressure was least in comparison to other two groups and it was statistically significant. (p<0.0.5) In our study, percentage fall in DBP from baseline in group MP was 13.69%, in group KP was 6.02% and in group C was 25.8% with p value <0.05 and was statistically significant. Abhimanyu Kalita et al in their study "A comparative study of small dose ketamine, midazolam and propofol as co-induction agent to propofol" found that the reduction in diastolic blood pressure was 9.15% in group KP, 15.01% in the MP group and 15.77% in the PP group.

Mean Arterial Pressure

In our study, mean arterial pressure was found to decrease in all the three study groups following induction. After co-induction the mean arterial pressure in Group KP is increased initially. In group KP change in MAP was least in comparison to other two groups and it was statistically significant. ($p<0.0.5$)

In our study, percentage fall in MAP from baseline in group MP was 12.26%, in group KP was 5.23% and in group C was 21.35% with p value <0.05 and was statistically significant. Abhimanyu Kalita et al in their study found that the fall in MAP was 7.39% in group KP, 12.60% in the MP group and 13.09% in the PP group.

Srivastava Uma et al in their study found that the fall in arterial pressure was minimum with ketamine group (4%) and maximum in control group (21%) Neelesh Nema et al in their study found that the fall in mean arterial pressure in the control group SP was 21.13% from baseline, in ketamine group KP was 4.57%, in midazolam group MP was 13.76%

CONCLUSIONS

In our study the groups were compared with regard to induction dose of propofol required, and hemodynamic variables. The following conclusions were made in our study:

- The induction dose of propofol was reduced in both Ketamine Propofol (KP) group as well as midazolam propofol (MP) group when compared to control group. However, the induction dose was least in Ketamine - Propofol (KP) group.
- There was greater change in heart rate, SBP, DBP and MAP in Midazolam Propofol (MP) group and in control group as compared to Ketamine Propofol (KP) group.
- Ketamine causes sympathetic stimulation, which counterbalances the cardiovascular effect of propofol.
- In our study, with doses of 0.4 mg/Kg ketamine, analgesic effect was also seen, and the major side effect of ketamine, which is dissociative anaesthesia, is eliminated with such small doses.

Thus, we conclude that co-induction with small dose ketamine 0.4 mg/Kg provides better haemodynamic stability with lesser induction dose of propofol as compared to midazolam. Therefore, ketamine can be preferred as co-induction agent to propofol.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Whitwam JG. Co-induction of anaesthesia: day-case surgery. European Journal of Anaesthesiology Supplement 1995;12:25-34.
[2] Kalita A, Ahmed AL. A comparative study of small dose of ketamine, midazolam and propofol as co-induction agent to propofol. Journal of Evidence Based Medicine and Healthcare 2017;4(64):3820-3825.
[3] Yadav RK, Bajracharya GR, Pokharel JN. Ketamine as an alternative to midazolam co-induction to propofol: a comparative study. Journal of Society of Anaesthesiologists of Nepal 2015;2(2):62-66.
[4] Kataria R, Singhal A, Prakash S, et al. A comparative study of efficacy of propofol auto-co-induction versus midazolam propofol co-induction using the priming principle. Indian Journal of Anaesthesia 2010;54(6):558-61.
[5] Butt MN, Ahmed A. The induction dose of propofol with ketamine-propofol and midazolam-propofol co-induction. J Anaesth Clin Res 2013;4:371.
[6] Rajkumar G, Thokchom R, Pradhan PC, et al. Co-induction effects of midazolam, thiopentone and ketamine with propofol in general anaesthesia. Journal of Medical Society 2013;27(2):110-113.
[7] Nema N, Arora KK, Rana A. A comparative study of small dose ketamine, midazolam and propofol as co-induction agent to propofol. Journal of Evolution of Medical and Dental Sciences 2014;3(47):11349-11357.
[8] Srivastava U, Sharma N, Kumar A, et al. Small dose propofol or ketamine as an alternative to midazolam co-induction to propofol. Indian J Anaesth 2006;50(2):112-114.