National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

# A prospective randomized controlled study to compare the efficacy of ephedrine and ketamine in the prevention of hypotension following propofol induction

**Gopakumar G[1], Prathibha V K[2], Ranju Jayaprakash[3]**

[1]Department of Anaesthesiology, Azeezia Institute of Medical Sciences, Kollam, Kerala, India, [2]Department of Pharmacology, Amala Institute of Medical Sciences, Thrissur, Kerala, India, [3]Department of Anaesthesiology, Royal Dental College, Chalissery, Palakkad, Kerala, India

**Correspondence to:** Prathibha V K. E-mail: prathibhaviswanathan@gmail.com

**Received:** May 24, 2020; **Accepted:** June 16, 2020

## ABSTRACT

**Background:** Propofol is the induction agent of choice for carrying out day care surgeries. Hypotension is one of its common adverse effects. Several drugs were evaluated in preventing this hypotension which gave inconclusive results. **Aims and objectives:** This study aimed to compare the efficacy of ephedrine and ketamine in preventing the hypotension due to induction with propofol. Its objective was to evaluate if ketamine has better efficacy than ephedrine in reducing the incidence of hypotension following propofol induction. **Materials and Methods:** We had done this randomized double-blind placebo controlled study prospectively in a total of 120 patients over 18 months. Patients planning to undergo elective surgeries under general anesthesia belonging to American Society of Anaesthesiologists (ASA) Grades 1 and 2 were incorporated in the study. They were divided into three groups after randomization. They were given normal saline (Group NS), ephedrine (Group ED), and ketamine (Group KA) just before administration of propofol for induction. Parameters such as non-invasive blood pressure (BP), heart rate (HR), and oxygen saturation were noted at baseline, 1 min after propofol administration, just before endotracheal intubation and at 1, 2, and 3 min after endotracheal intubation. The efficacies of drugs were assessed based on variation in BP and HR. **Results:** In this study, the systolic, diastolic, and mean arterial pressure values in group KA and group ED after propofol injection and before endotracheal intubation were considerably higher than that of group NS ($P < 0.001$). The mean HR values in the three groups were similar ($P > 0.05$). **Conclusion:** Ephedrine and ketamine have similar efficacy in reducing the incidence of hypotension following induction with propofol.

**KEY WORDS:** Ephedrine; Ketamine; Propofol; Hypotension

## INTRODUCTION

Propofol is the preferred drug for induction of anesthesia especially for daycare surgeries and in situations where a supraglottic airway is to be used. It is extensively used for induction of general anesthesia because of its rapid onset of action.[1] When compared to thiopentone sodium, it delivers superior quality of anesthesia and has the advantage of rapid recovery. Hypotension and pain on injection are the common disadvantages of propofol injection.[2]

| Access this article online | |
|---|---|
| **Website:** www.njppp.com | Quick Response code |
| **DOI:** 10.5455/njppp.2020.10.06145202016062020 | |

Propofol can reduce the systolic and diastolic arterial pressures by 25–30% from the baseline due to a decrease in systemic vascular resistance or cardiac output or both and decrease in heart rate (HR) due to increased vagal activity.[2] They also occur as a result of depressed myocardial contractility

and impaired baroreflex mechanism.[3,4] The influence of hemodynamic aberrations during anesthesia on adverse outcomes is an important clinical issue.[5]

Various drugs have been evaluated in the prevention of hypotension following propofol injection with inconclusive results. Preloading with crystalloid and colloid solutions have also been tried to inhibit the occurrence of hypotension after propofol injection.[6,7] Several studies were done using ketamine, ephedrine, atropine, glycopyrrolate, metaraminol, dopamine, and dobutamine to prevent this hypotension which showed variable outcomes.[8-11]

Ephedrine is commonly administered during spinal and epidural anesthesia to overcome the hypotension and bradycardia. This is because of its direct action on the adrenergic receptors and indirect action involving release of endogenous norepinephrine. Ketamine is an intravenous anesthetic agent with unique effects on the cardiovascular system. It stimulates the cardiovascular system leading to an increase in blood pressure (BP), HR, and cardiac output. Only few studies have addressed the effect of ketamine in decreasing the incidence of hypotension due to propofol injection.

This research was done to assess the efficacy of small doses of ketamine and ephedrine in preventing the hypotension following injection of propofol. The objective of this research was to evaluate if ketamine has better efficacy than ephedrine in preventing the hypotension. This study also analyzed the effect of ketamine and ephedrine on HR.

## MATERIALS AND METHODS

### Study Design

This randomized double-blind placebo controlled research was done prospectively in 120 patients over 18 months at a tertiary care hospital. It was initiated following approval from the Institutional Review Board. We included patients between 20 and 60 years of age posted for planned surgeries to be done under general anesthesia. Patients who belonged to American Society of Anaesthesiologists (ASA) Grades 1 and 2 were included in the study. Those with weight <45 kg, history of hypertension or heart disease, history of epilepsy, cerebrovascular accident or conditions with raised intracranial pressure, allergic history to ED, KA, propofol and pregnant ladies were not included in this study.

### Study Procedure

Patients for the study were selected after satisfying the inclusion, exclusion criteria, and pre-anesthesia evaluation was performed. Written informed consent was taken. Study subjects were allocated into three sets of 40 each after randomization using computer generated tables – normal saline (NS) group where the patients were given NS 2 ml, ED group where patients were given ephedrine 0.07 mg/kg, KA group where they were given ketamine 0.5 mg/kg just before administration of propofol for induction.

The whole procedure was explained to the patients on the pre-operative day and they were asked to remain nil oral 6 h before surgery. They were administered oral diazepam 0.2 mg/kg body weight, oral ranitidine 150 mg, and oral metoclopramide 10 mg on the pre-operative night and on the morning 1 h before surgery as per institutional protocol. A complete check of the anesthesia machine, circuit, and equipment including arrangement of the emergency drugs was done.

An intravenous cannulation was done in a large vein using 18 gauge cannula 20 min before anesthetic induction and ringer lactate solution was infused. Monitors were connected to patients and baseline parameters such as oxygen saturation, HR, and non-invasive BP were recorded. The solutions of test drugs to be given were prepared in identical plastic syringes 15 min before induction by a doctor who was not part of this study and labels were masked. This was done to make sure that the clinician who assessed the patient response was not aware of the test drug. After preoxygenation, the drug being tested was administered over 5 s followed immediately by propofol 2.5 mg/kg (10 mg/ml) injected through three-way connected to intravenous catheter slowly over 30 s. Afterwards, ringer lactate was administered. After propofol injection and loss of consciousness, vecuronium 0.12 mg/kg was given. It was followed by intermittent positive pressure ventilation with oxygen 6 L/min and 1.5% isoflurane by a facemask. After 3 min, direct laryngoscopy and endotracheal intubation were carried out. The position of tube was confirmed and kept secure. Maintenance of anesthesia was done with oxygen nitrous oxide 1:2 ratio at fresh gas flow of 4 L/min and 0.5% isoflurane. Fentanyl 1.5 mcg/kg was given for analgesia.

HR and non-invasive BP were noted at the beginning, 1 min after propofol injection, immediately before endotracheal intubation and 1, 2, and 3 min after endotracheal intubation. Oxygen saturation was also recorded. Intraoperatively, muscle relaxation was maintained with top up doses of vecuronium. After surgery, neuromuscular blockade was reversed after administering intravenous neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. Extubation of patients was performed after complete reversal. Then, the patients were transferred to the post-operative unit and monitored.

### Analysis of Statistical Data

The data collected were entered into a master chart. Data were analyzed statistically using Statistical Package for the Social Sciences version 20. Descriptive statistics were used for quantitative variables, namely, mean and standard deviation. Comparison of the categorical variables between the groups was done using Chi-square test. Analysis of variance (One-Way ANOVA) was done to compare different variables

between groups as well as to compare observations within each group. Duncan's multiple range test was also done along with ANOVA to elucidate comparisons between each group within each parameter. For all the statistical evaluations done, $P < 0.050$ was considered significant.

## RESULTS

In this study, three groups of patients with 40 patients in each group posted for planned surgeries to be done under general anesthesia were studied for 18 months. They were administered NS (group NS), ephedrine 0.07 mg/kg (group ED), and ketamine 0.5 mg/kg (group KA) just before the injection of 2.5 mg/kg propofol. The three groups were similar with regard to age, weight, and sex with no statistically considerable difference ($P > 0.050$). No significant differences were noted in HR, systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) between three study groups preoperatively ($P > 0.050$), as shown in Table 1.

### Comparison between Groups after Propofol Injection and Before Intubation

The values of MAP, SBP, DBP of ED, and KA groups were found to be considerably higher than NS group after propofol injection and before intubation with $P < 0.001$. No considerable difference in HR was noted among the three groups ($P > 0.050$). Notable differences were not observed between groups ED and KA ($P > 0.050$) [Tables 2 and 3].

### Comparison between Groups 1 Min after Intubation

The SBP, DBP, MAP values of ED, and KA groups were considerably higher ($P < 0.001$) than NS group 1 min after endotracheal intubation. Mean HR was also higher in ED group compared to NS group but was not statistically significant. Mean DBP was also higher but was not statistically significant. SBP and HR were notably higher in ED group on comparing with KA group 1 min after endotracheal intubation. HR 1 min after endotracheal intubation was significantly higher in ED group than KA group ($P < 0.050$) [Figure 1].

### Comparison between Groups 2 Min after Intubation

The SBP, DBP, and MAP values 2 min after intubation were significantly higher in groups ED and KA on comparison with group NS ($P < 0.001$). No considerable differences were noted between group ED and KA ($P > 0.060$). No considerable difference in HR was noted between the three groups 2 min after endotracheal intubation ($P > 0.050$) [Figure 2].

**Table 1:** Comparison of pre-operative baseline BP and heart rate in between groups

| Parameter | Group | Mean±SD | F value | *P* value |
|---|---|---|---|---|
| Systolic BP | NS | 124.15[a]±7.07 | 0.482 | >0.05 |
| | ED | 124.48[a]±7.22 | | |
| | KA | 123.03[a]±6.47 | | |
| Diastolic BP | NS | 78.20[a]±5.34 | 0.188 | >0.05 |
| | ED | 78.60[a]±5.48 | | |
| | KA | 78.93[a]±5.08 | | |
| Mean arterial pressure | NS | 93.40[a]±5.65 | 0.067 | >0.05 |
| | ED | 93.86[a]±5.85 | | |
| | KA | 93.59[a]±5.47 | | |
| Heart rate | NS | 73.88[a]±3.84 | 0.671 | >0.05 |
| | ED | 74.25[a]±2.73 | | |
| | KA | 73.48[a]±2.15 | | |

[a]Means with same superscript do not differ each other with in each parameter (Duncan's Multiple Range Test). BP: Blood pressure, NS: Normal saline, ED: Ephedrine, KA: Ketamine

**Table 2:** Comparison of BP, heart rate between groups after propofol injection

| Parameter | Group | Mean±SD | F value | *P* value |
|---|---|---|---|---|
| Systolic BP | NS | 107.83[a]±5.38 | 32.221 | <0.001 |
| | ED | 115.95[b]±5.93 | | |
| | KA | 117.38[b]±5.90 | | |
| Diastolic BP | NS | 66.15[a]±5.48 | 26.988 | <0.001 |
| | ED | 72.40[b]±4.95 | | |
| | KA | 74.03[b]±4.73 | | |
| Mean arterial pressure | NS | 80.17[a]±4.96 | 30.981 | <0.001 |
| | ED | 86.88[b]±5.08 | | |
| | KA | 88.44[b]±4.93 | | |
| Heart rate | NS | 76.13[a]±4.05 | 1.463 | >0.05 |
| | ED | 76.43[a]± 2.54 | | |
| | KA | 75.28[a]± 2.52 | | |

[a,b]Means with same superscript do not differ each other with in each parameter (Duncan's Multiple Range Test). BP: Blood pressure, NS: Normal saline, ED: Ephedrine, KA: Ketamine

**Table 3:** Comparison of BP, heart rate between groups before intubation

| Parameter | Group | Mean±SD | F value | *P* value |
|---|---|---|---|---|
| Systolic BP | NS | 103.45[a]±5.49 | 89.891 | <0.001 |
| | ED | 118.40[b]±5.92 | | |
| | KA | 118.43[b]±5.87 | | |
| Diastolic BP | NS | 62.25[a]±7.89 | 53.778 | <0.001 |
| | ED | 74.75[b]±4.96 | | |
| | KA | 74.25[b]±5.00 | | |
| Mean arterial pressure | NS | 75.95[a]±6.70 | 71.533 | <0.001 |
| | ED | 89.24[b]±5.11 | | |
| | KA | 89.03[b]±5.13 | | |
| Heart rate | NS | 76.30[a]±3.80 | 1.696 | >0.05 |
| | ED | 75.13[a]±2.15 | | |
| | KA | 75.40[a]±2.76 | | |

[a,b]Means with same superscript do not differ each other with in each parameter (Duncan's Multiple Range Test). BP: Blood pressure, NS: Normal saline, ED: Ephedrine, KA: Ketamine

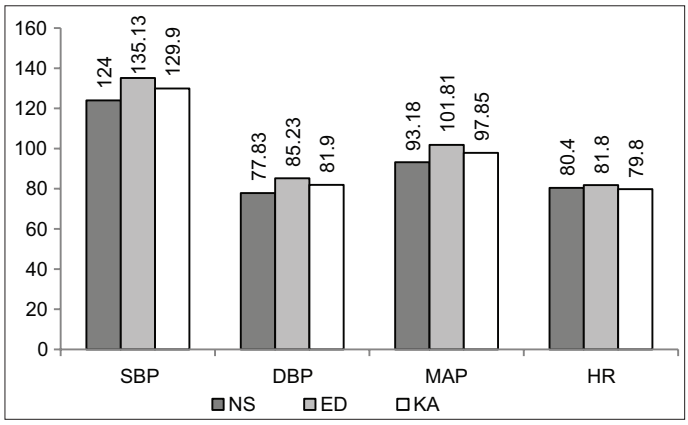


**Figure 1:** Comparison of blood pressure, heart rate in three groups 1 min after intubation

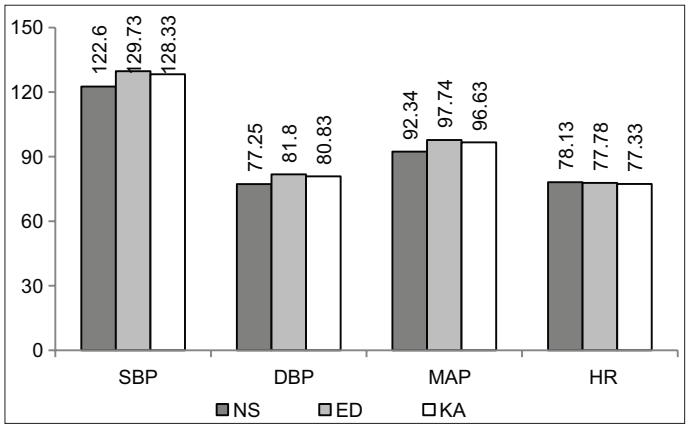


**Figure 2:** Comparison of blood pressure, heart rate in three groups 2 min after intubation

### Comparison between Groups 3 Min after Intubation

There were no considerable differences in HR, SBP, DBP, and MAP between the three study groups 3 min after endotracheal intubation ($P > 0.050$) although the mean values were higher in groups ED and KA compared to group NS, as shown in Figure 3.

### Comparison of Hemodynamic Variables within Groups

Significant reduction in SBP, DBP, and MAP was noted in group NS after propofol injection and before endotracheal intubation on comparing with the baseline ($P < 0.001$). There was considerable increase in HR 1 min following endotracheal intubation compared to baseline in NS group. The mean SBP, DBP, and MAP values were lowest after propofol injection and before intubation in the ED group. One minute after intubation, the mean SBP, MAP, and HR were noted to be highest whereas mean DBP was highest 2 min after intubation in group ED. Mean SBP, DBP, and MAP values were lowest after propofol injection and before intubation in KA group as well. The mean SBP, DBP, MAP, and HR values were highest 1 min after intubation in KA group.

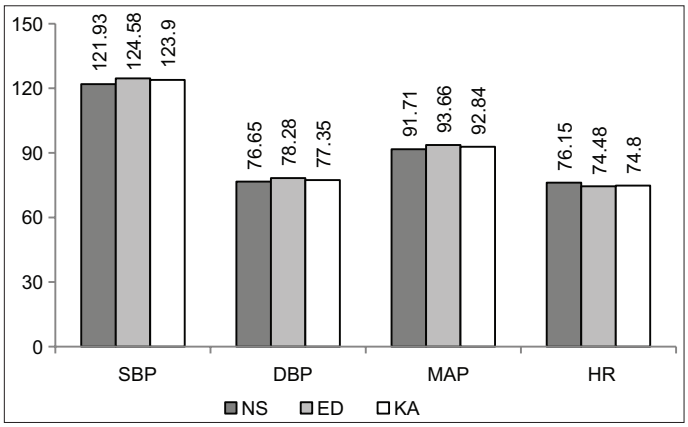


**Figure 3:** Comparison of blood pressure, heart rate in three groups 3 min after intubation

## DISCUSSION

Hypotension is a frequent adverse effect seen with the use of propofol which is the favored intravenous induction agent in outpatient anesthesia. Several drugs were evaluated in preventing this hypotension which gave inconclusive results. This research was conducted to ascertain if ephedrine or ketamine pretreatment in low doses could reduce the hypotension due to propofol administration and to evaluate if ketamine has better efficacy than ephedrine.

The present study validates that induction of anesthesia with propofol in ASA Grades 1 and 2 patients is often linked to systemic hypotension. None of the patients in any groups experienced severe hypotension. In this study, the values of systolic, diastolic, and MAP in groups ketamine and ephedrine after the injection of propofol and before endotracheal intubation were considerably higher when compared to Group NS. There was no considerable difference between the three groups with respect to HR. However, both ephedrine and ketamine were not completely effective in preventing the likelihood of hypotension after propofol administration. This study confirmed that there was no statistically significant difference among groups ED and KA in preventing the hypotension.

The decrease in BP and HR following induction with propofol is due to fall in peripheral vascular resistance, inhibition of myocardial contractility and inhibition of sympathetic system resulting in a decrease in cardiac output and vascular resistance.[12] Ketamine causes stimulation of sympathetic system due to an increase in HR and BP.[12] According to Furuya *et al*.,[12] Ketamine when given in a dose of 0.5 mg/kg just 1 min before propofol induction could prevent the significant fall in BP before endotracheal intubation and considerable increase in BP after endotracheal intubation. Cheong *et al*.[13] opined that 30 mcg/kg and 70 mcg/kg of ephedrine avoided the occurrence of hypotension following propofol induction without notable change in hemodynamics. In view of the slightly higher MAP values, we preferred to use 70 mcg/kg ephedrine in this study. Hemmingsen and Neilsen[14] mentioned

that administration of 0.7 mg/kg of ketamine as bolus dose before subarachnoid block had elevated MAP on comparison with another group given 1.5 mcg/kg fentanyl. Similarly, a study done by Hui *et al*.[15] suggested that ketamine when combined with propofol for anesthetic induction compensated the cardiodepressant effects of propofol without significant effect on HR due to its cardiostimulant effects. The findings of our study are consistent with that of the above-mentioned studies. Desaturation was not experienced by any of the patients in our study groups.

Our study could establish that ephedrine 0.07 mg/kg and ketamine 0.5 mg/kg are effective in inhibiting the occurrence of hypotension linked with propofol induction. It also showed that both ephedrine and ketamine had almost equal efficacy in preventing the hypotension. It clearly showed that ketamine did not offer any added advantage over ephedrine for this purpose.

## CONCLUSION

Ephedrine and ketamine are effective in inhibiting the occurrence of hypotension linked with propofol induction. The efficacy of ketamine in preventing the incidence of hypotension on induction with propofol is equivalent to that of ephedrine.

## ACKNOWLEDGMENTS

We acknowledge the support extended by the Department of Anaesthesiology, Azeezia Institute of Medical Sciences, Kollam and the Department of Pharmacology, Amala Institute of Medical Sciences, Thrissur, in the successful completion of the study and preparation of manuscript. We thank Dr Venugopal, Additional Professor in Anaesthesiology, RCC, Thiruvananthapuram for his valuable guidance.

## REFERENCES

1. Smith I, White PF, Nathanson M, Gouldson M. Propofol. An update on its clinical use. Anaesthesiology 1994;81:1005-43.
2. Morgan EG, Mikhail MS Murray MJ. Clinical Anaesthesiology. 3rd ed. New York, USA. The McGraw and Hill Companies; 2002. p. 173.
3. Robinson BJ, Ebert TJ, O'Brien TJ, Colinco MD, Muzi M. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? Anaesthesiology 1997;86:64-72.
4. Cullen PM, Turtle M, Prys-Roberts C , Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115-20.
5. Reich D L, Hossain S, Krol M, Baez B, Patel P, Bernstein A, *et al*. Predictors of hypotension after induction of general anaesthesia. Anaesth Analg 2005;101:622-8.
6. Turner RJ, Gatt SP, Kam PC, Ramzan I, Daley M. Administration of a crystalloid fluid preload does not prevent the decrease in arterial blood pressure after induction of anaesthesia with propofol and fentanyl. Br J Anaesth 1998;80:737-41.
7. Al-Gamdi A. Hydroxyethylstarch 6% preload does not prevent the hypotension following induction with propofol and fentanyl. Middle East J Anaesthesiol 2004;17:959-68.
8. Ozkocak I, Aitunkaya H, Ozer Y, Ayoğlu H, Demirel CB, Çiçek E. Comparison of ephedrine and ketamine in prevention of injection pain and hypotension due to propofol induction. Eur J Anaesthesiol 2005;22:44-8.
9. Skues MA, Richards MJ, Jarvis AP, Prys-Roberts C. Preinduction atropine or glycopyrrolate and hemodynamic changes associated with induction and maintenance of anesthesia with propofol and alfentanil. Anesth Analg 1989;69:386-90.
10. Kasaba T, Yamaga M, Iwasaki T, Yoshimura Y, Takasaki M. Ephedrine, dopamine, or dobutamine to treat hypotension with propofol during epidural anesthesia. Can J Anaesth 2000;47:237-41.
11. Chiu CL, Tew GP, Wang CY. The effect of prophylactic metaraminol on systemic hypotension caused by induction of anaesthesia with propofol in patients over 55 years. Anaesthesia 2001;56:893-7.
12. Furuya A, Matsukawa T, Ozaki M, Nishiyama T, Kume M, Kumazawa T. Intravenous ketamine attenuates arterial pressure changes during the induction of anaesthesia with propofol. Eur J Anaesthesiol 2001;18:88-92.
13. Cheong MA, Kim KS, Choi WJ. Ephedrine reduces the pain from propofol injection. Anesth Analg 2002;95:1293-6.
14. Hemmingsen C, Neilsen JE. Intravenous ketamine for prevention of severe hypotension during spinal anaesthesia. Acta Anaesthesiol Scand 1991;35:755-7.
15. Hui TW, Short TG, Hong W, Suen T, Gin T, Plummer J. Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. Anaesthesiology 1995;82:641-8.

**How to cite this article:** Gopakumar G, Prathibha VK, Jayaprakash R. A prospective randomized controlled study to compare the efficacy of ephedrine and ketamine in the prevention of hypotension following propofol induction. Natl J Physiol Pharm Pharmacol 2020;10(08):671-675.

**Source of Support:** Nil, **Conflicts of Interest:** None declared.