PROPHYLACTIC USE OF EPHEDRINE TO ATTENUATE THE HAEMODYNAMIC RESPONSES TO PROPOFOL

M. Mahesh[1], A. Sanjeev Rao[2]

[1]Assistant Professor, Department of Anaesthesiology, Fathima Institute of Medical Sciences, Kadapa.
[2]Civil Surgeon, Department of Anaesthesiology, ESI Hospital, Sanath Nagar, Hyderabad, Telangana.

ABSTRACT

BACKGROUND
The beginning of anaesthesia since October 16th 1846.

THE ETHER DAY
Inhalational methods had dominated the practice of Anaesthesia. The most important factor in the increasing popularity of intravenous anaesthesia has been the availability of PROPOFOL since 1980s. Over a period of time it has become the drug of choice for induction. But, the hypotension induced by Propofol has been a matter of concern.

AIM OF STUDY
To study the prophylactic use of ephedrine to attenuate the haemodynamic responses to propofol.

MATERIALS AND METHODS
Sixty patients belonging to ASA grade I and II belonging to either sex were included in the study. They were aged between 20-50 years. These patients were randomly divided into two groups. Group I included patients who received 2mg/kg Propofol as induction dose and group II received 20mg ephedrine 2 min before induction with 2mg/kg Propofol.

RESULTS
Fall in blood pressure was found in both the groups but, the fall was statistically insignificant in Group II who received ephedrine.

CONCLUSION
The prophylactic use of ephedrine significantly attenuated the decrease in blood pressure associated with induction of anaesthesia with propofol.

KEYWORDS
Propofol, Ephedrine, Hypotension, Vasopressor.

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INTRODUCTION: Propofol is most commonly used intravenous anaesthetic agent, it has rapid onset of action, smooth induction and rapid recovery. Propofol is primarily hypnotic, duration of hypnosis is dose dependent. Propofol alters mood following short surgical procedure to a lesser extent than thiopentone. But the most prominent effect of propofol is decrease in arterial blood pressure during induction of anaesthesia. The decrease in arterial pressure is associated with decrease in cardiac output, stroke volume index, and systemic vascular resistance. Propofol inhibits the baroreflex, thus reducing tachycardic response to hypotension. Induction of Anaesthesia with propofol has been shown to have potent haemodynamic effects, dominated by hypotension. Several underlying mechanisms-such as myocardial depression and decrease in afterload[1,2] or preload[3,4] have been suggested.

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Corresponding Author:
Dr. M. Mahesh,
Flat No. 202, Palace Heights Apartments,
Near Netaji Statue, Ayodhya Nagar,
Dr. A. S. Rao Nagar, Secunderabad-62.
E-mail: dr.mahi99@gmail.com
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Ephedrine is a vasopressor commonly used during anaesthesia to counteract the decrease in arterial blood pressure and heart rate after spinal and general anaesthesia.[5] In addition to its alpha vasoconstrictor and beta cardio-stimulant effects, it also has the advantage of being short lived, so has a similar action profile like propofol. In 1998, Michelson Iver, Soren H, Honsen H et all studied that prophylactic ephedrine attenuates the hemodynamic response to propofol in elderly female patients. In this study, ninety patients aged 60 yrs. or older were randomly allocated to one of three groups of 30 patients each to receive either normal saline, ephedrine 10 mg, or ephedrine 20 mg i.v. 1 min before the induction of anaesthesia. The decrease in blood pressure and heart rate (HR) was significantly less in each of the ephedrine groups. Furthermore, the decrease was less in the large-dose group compared with the small-dose group. In conclusion, the prophylactic injection of ephedrine significantly attenuated, but did not completely abolish, the decrease in blood pressure associated with induction of anaesthesia with fentanyl and propofol. Ephedrine 20 mg was slightly more effective than ephedrine 10 mg.

AIM OF THE STUDY: The aim of this prospective, placebo controlled, double blind, randomized trial was to determine the efficacy of prophylactic dose of ephedrine against the anticipated propofol induced hypotension.

MATERIALS AND METHODS: After obtaining the Ethical committee of Fathima Institute of Medical Sciences (NTR University of health sciences) approval and informed consent, sixty patients (between ages of 20 to 50 years) of either sex of ASA grade I or II, scheduled for elective surgery under general anaesthesia were included in the study.

Exclusion criteria included patients with a history of;

1. Allergy to the study medications
2. Uncontrolled cardiovascular, respiratory, renal and hepatic diseases
3. Controlled or uncontrolled hypertension
4. Therapy with diuretics or vasoactive medications
5. Morbid obesity
6. Pregnancy

The study was designed assuming a change of 10mmHg in the systolic blood pressure from the Base line in any of the study groups in comparison to the placebo group to provide more than 80% power for the two tail t test at the level of 5% significance. A minimum sample size of 30 patients was determined in each group.

Patients were premedicated with injection midazolam 1-2 mg and injection ondansetron 4 mg. After base line haemodynamic measurements, Inj. Tramadol 1-2 mg/kg was administered as bolus.

All the study medications were prepared in identical syringes and in the equal volume (2 ml) and neither the observer nor the patient was aware about the drug.

Patients were randomly allocated to one of the two groups using a table of random numbers as following.

Group I: (n= 30) patients received normal saline intravenously as placebo 2 minutes before induction followed by propofol.

Group II: (n= 30) patients received ephedrine 20 mg intravenously 2 minutes before induction followed by propofol.

Patient was induced 2 minutes after the study medication by using propofol 2 mg/kg given over 30 seconds until loss of consciousness and verbal response. Patients breathed 100% oxygen and respiration was assisted by mask if apnoea occurred.

The endotracheal intubation was facilitated with injection succinyl choline 1.5 mg/kg. The anaesthesia was maintained with 60% nitrous oxide in oxygen and 0.5% halothane mixture along with Inj. Vecuronium 0.05 mg/kg as per the requirement of the patient. All the patients were monitored using ECG, pulse oximetry, NIBP.

Haemodynamic variables like heart rate, systolic, diastolic and mean arterial blood pressure were measured before induction[as base line],and at 2,5,10,30,60 minutes after induction. After completion of surgery, neuromuscular blockade was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01mg/kg.

Rescue ephedrine I.V (20 mg) was given to the patient if the systolic blood pressure fell below 80 mmHg or there was more than 20% decrease in systolic blood pressure from the baseline. Rescue atropine I.V. 0.6 mg was given to the patients if the heart rate decreased below 50 per minute.

OBSERVATIONS AND RESULTS: The study was conducted in sixty ASA grade I and II patients of either sex undergoing general surgical procedures. The results obtained were statistically analyzed using student 't' test and significance ascertained with p values. Paired 't' test was used within the group comparison and unpaired 't' test for between the groups comparison.

There were no significant differences among groups in terms of age, sex, weight and ASA grade.

Groups	I (n=30)	II (n=30)
Age (in year)	31.6±6.86	31.1±5.88
Sex (M:F ratio)	18:12	15:15
Weight (in kgs)	60.12±5.13	57.52±6.34
ASA Class (I/II)	18:12	17:13

Table 1: Demographic data of the patients

Values are being represented as Mean±SD. or ratio.
n = Number of patients in each group.

Groups	Baseline	2 mins	5 mins	10 mins	30 mins	60 mins
Group-I						
HR	82.0±9.23	81.1±18.76*	89.9±18.76*	84.1±13.92	78.5±13.26	78.6±18.42
SBP	129.0±9.85	87.6±10.45*	107.0±9.2*	104.0±8.73*	109.2±8.78*	114.4±10.87*
DBP	80.8±6.05	57.4±5.95*	74.4±6.16*	71.8±6.2*	75.6±6.55*	78.6±5.9
MAP	97.7±5.59	67.6±6.92*	85.2±6.98*	81.6±6.61*	87.2±7.46*	90.7±7.5*
Group-II						
HR	84.4±7.89	103.91±7.99*	107.2±9.59*	102.5±5.61	94.2±8.87	86.3±4.71
SBP	122.8±8.04	132.0±5.3	131.9±9.52	129.0±9.56	124.0±8.19	123.8±7.1
DBP	77.2±5.77	82.6±4.18	83.6±4.88	78.0±5.68	78.8±4.66	79.0±5.32
MAP	92.3±6.81	98.6±4.34*	99.7±5.09*	96.0±5.17	94.2±3.93	92.3±5.55

Table 2: Haemodynamic variables at different time intervals

Abbreviations: HR-Heart rate, SBP – Systolic blood pressure, DBP- Diastolic blood pressure, MAP – Mean arterial pressure.

Values are being represented as Mean±SD.

*p<0.05 – comparison within the group from baseline.

All the two groups were comparable with regard to baseline haemodynamic variables. There was a significant increase in heart rate from baseline till 30 minutes in group II.

The SBP, DBP and MAP showed a significant decrease from the baseline in group I at different time intervals (P<0.05). In group II the SBP and MAP significantly increased till 10 minutes (P<0.05), while DBP was significantly increased till 5 minutes only (p<0.05). Although, until the whole study period, group II showed an increase in SBP, DBP and MAP. There was a significant difference among the groups regarding the change in SBP and MAP at different time intervals (p<0.05). On comparing the DBP among the groups, the change was significant, between group I and group II at different time intervals.

The number of patients who experienced a decrease in SBP to <80 mmHg was less in ephedrine group (p<0.05) (table-2). Consequently, fewer patients in the ephedrine group received rescue ephedrine. Similarly significantly less number of patients required rescue atropine in the ephedrine group as compared to the placebo.

DISCUSSION: The ideal profile for a single anaesthetic agent includes a rapid onset of anaesthesia, short duration of action, lack of cumulation on repeated administration and absence of excitatory effects during induction and recovery with minimal intra and post-operative sequelae. Till date, no such ideal agent is present. But, propofol has been shown to have many of these properties but prophylactic pre-treatment of I.V. ephedrine prevents the decrease in blood pressure and heart rate in doses of 20 mg in individuals of ASA class I and II.

Considering the cardiovascular effects of the drugs used in the study - The cardiovascular effects of propofol have been evaluated following its use both for induction and for maintenance of anaesthesia. The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anaesthesia. Independently of the presence of cardiovascular disease, an induction dose of 2 to 2.5mg/kg produces a 25 to 40% reduction of systolic blood pressure. Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index (15%), stroke volume index (20%), and systemic vascular resistance (15-25%). Left ventricular stroke work index is also decreased by (30%). The decrease in systemic pressure following an induction dose of propofol appears to be due to both vasodilation and myocardial depression. Both the myocardial depressant effect and the vasodilation appear to be dose-dependent and plasma concentration –dependent. Heart rate does not change significantly after an induction dose. Propofol inhibits the baroreflex, thus reducing the tachycardic response to hypotension.

Cardio vascular effects of ephedrine resemble those of epinephrine, but its systemic blood pressure elevating response is less intense and lasts approximately 10 times longer. It requires approximately 250 times more ephedrine than epinephrine to produce equivalent blood pressure response. IV administration of ephedrine results in increase in systolic and diastolic blood pressure, heart rate and cardiac output.

Renal and splanchnic blood flows are decreased whereas coronary and skeletal blood flows are increased. Systemic vascular resistance may be altered minimally because vasoconstriction in some vascular beds is offset by vasodilatation in other areas. (BETA 2 stimulation.)These cardiovascular effects are due in part to alpha receptor mediated peripheral arterial and venous vasoconstriction.

The principle mechanism, however, for cardiovascular effects produced by ephedrine is increased myocardial contractility due to activation of beta 1 receptors.

In the presence of pre-existing beta adrenergic blockade, the cardiovascular effects of ephedrine may resemble responses more typical of alpha adrenergic receptor stimulation. A second dose of ephedrine produces a less intense systemic blood pressure response than the first dose. This phenomenon is known as tachyphylaxis, occurs with many sympathomimetics and is related to duration of action of these drugs.

The hypotensive effect of propofol is dose dependent[6] and furthermore it is more pronounced in patients more than 60 years of age, even if, the increased sensitivity to propofol in elderly is considered.[7] We have conducted our trial on patients aged 20-50 years and dose used was 2.0 $mgkg^{-1}$ body weight. Propofol concentration required for suppression of responses to surgical stimulus are much higher than those required for loss of consciousness[7]. However, propofol requirement for skin incision is reduced, and surgical conditions improved, when propofol is supplemented by an opioid.[7,8] It has been claimed that reduction in blood pressure after propofol could be less if rate of administration of propofol is reduced to 50 $mgmin^{-1}$.[9] However, this is most probably due to smaller doses used in low rate group.[6] It is possible that incidence of hypotension in the present study would have been less, had we used a smaller dose of propofol.

Rapid sequence intubation with propofol has been shown to produce significant fall in blood pressure and some authors suggested a pressor and some authors suggested a preoperative volume loading with Ringer's lactate to antagonise propofol induced hypotension without any increments in heart rate.[10]

Prophylactic ephedrine has been used to attenuate the haemodynamic response to propofol in elderly female patients and it was found that 0.1 or 0.2 $mgkg^{-1}$ ephedrine I.V. markedly attenuated the decrease in blood pressure but neither of them abolished it.[11] In our study we have used prophylactic dose of ephedrine 20 mg I.V. The 20 mg I.V. ephedrine completely abolishes the haemodynamic responses to propofol.

Haemodynamic effects of propofol in combination with ephedrine have been evaluated in elderly patients (ASA group III and IV) and due to the risk of tachycardia inducing myocardial ischemia in this group of patients, the authors did not recommend the use in elderly patients of any of the ephedrine/propofol mixture.[12] The increase in heart rate is not hazardous in our group of patients as they were young and belonging to ASA physical status I and II.

In one of the recent studies, it was found that in anaesthetized patients premedicated with clonidine, decrease in blood pressure may be easier to reverse with ephedrine after propofol anaesthesia.[13] Our finding also coincides with them.

A reverse study in comparison to ours has been conducted and it was concluded that the magnitude of pressor responses to ephedrine during propofol anaesthesia were significantly greater than during the awake state. However, ephedrine 0.1 $mgkg^{-1}$ I.V. showed no significant increase in blood pressure during sevoflurane anaesthesia; so propofol, not sevoflurane anaesthesia augments the pressor response to I.V. ephedrine.[14]

SUMMARY AND CONCLUSION: The objective of the study was to determine the efficacy of prophylactic dose of ephedrine against the anticipated propofol induced hypotension in patients scheduled for various surgical procedures under general anaesthesia. Sixty patients, aged 20-50 years of both sex belonging to ASA grade I and II; were randomly allocated in to two groups of 30 patients each to receive either normal saline or ephedrine 20 mg IV 2 minutes prior to induction of anaesthesia. The anaesthesia was induced with 2 mg/kg bolus dose of propofol IV given over 30 seconds.

Haemodynamic variables were measured before and at 2, 5,10,30,60 minutes after induction. The decrease in blood pressure, heart rate was significantly less in ephedrine group ($p < 0.05$).

In conclusion, the prophylactic use of ephedrine significantly attenuated the decrease in blood pressure associated with induction of anaesthesia with propofol.

The present study confirms that induction of anaesthesia with propofol in doses of 2 $mgkg^{-1}$ as bolus is often associated with significant systemic arterial hypotension and bradycardia. Ephedrine was found to be effective at obtunding the hypotensive response to bolus propofol induction with minimum over shoots in response, confirming its safety in young healthy patients. In the groups we studied the most appropriate dose seems to be 20 mg I.V. for 2 $mgkg^{-1}$ bolus dose of propofol.

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