

The effect of prophylactic phenylephrine on systemic hypotension during induction of anaesthesia with propofol in patients over 55 years old

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ABSTRACT

Background: Induction of anaesthesia with propofol is often associated with a significant decrease in arterial pressure, especially in the older population. The aim of this study is to determine the efficacy of phenylephrine in two different doses i.e. 100mcg and 200mcg, given during induction to counteract the anticipated hypotensive effect of propofol in older patients aged over 55 years.

Methods: Seventy-two ASA physical status I – II patients aged 55 years or older were randomly allocated to group 1 (received propofol mixed with normal saline), group 2 (propofol mixed with 100mcg of phenylephrine) or group 3 (propofol mixed with 200mcg of phenylephrine). Anaesthesia was induced with fentanyl 1.5mcg/kg and propofol 2mg/kg (mixed with the study drug). Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded at 1 minute intervals for up to 5 minutes after induction.

Results: SBP, MAP and DBP decreased significantly after induction in the control group and group 2 (phenylephrine 100mcg). In contrast, SBP was maintained to near baseline for the first two minutes after induction using phenylephrine 200mcg in group 3, and similar trends were seen with MAP and DBP at a lesser magnitude.

Conclusion: Phenylephrine 200mcg is more effective than 100mcg in attenuating propofol induced hypotension, especially during the first two minutes after induction, in patients aged 55 years and above.

KEY WORDS:

Phenylephrine, propofol, hypotension, induction of anaesthesia, aged 55 years old

INTRODUCTION

Propofol has emerged as the main intravenous induction agent in current clinical practice, owing to its many advantages over other agents; e.g. quicker recovery, minimal hangover effects, less postoperative nausea and vomiting, earlier return of psychomotor function, etc.

Induction of anaesthesia with propofol is often associated with a significant decrease in arterial pressure.¹ The

hypotensive effect of propofol has been attributed to a decrease in systemic vascular resistance and/or cardiac output caused by a combination of venous and arterial vasodilation, impaired baroreceptor reflex mechanism and depression of myocardial contractility. These adverse effects are especially marked in older patients due to their reduced ability to make compensatory changes.² Hypotension in these patients may reduce tissue perfusion and oxygenation to critical levels.

Various methods have been attempted to prevent or attenuate the hypotensive effect of propofol during induction of anaesthesia, including administering a fluid preload and prophylactic use of vasopressors. Fluid preload was found to be ineffective in preventing propofol induced hypotension.³ Ephedrine, an alpha and beta adrenergic agonist was the main vasopressor investigated in previous studies in both young and older populations.⁴⁻⁶ One study evaluated the efficacy of metaraminol, a predominant alpha agonist, on propofol induced hypotension in patients more than 55 years old and showed that metaraminol 0.5mg did not prevent hypotension in these patients.⁷

Phenylephrine is a synthetic non-catecholamine that stimulates principally alpha-1 adrenergic receptors directly. A small part of its pharmacological response is due to its ability to release noradrenaline (indirect actions). It has minimal effect on beta-adrenergic receptors. Phenylephrine has been proven in various studies as an effective vasopressor to maintain arterial blood pressure during spinal anaesthesia for Caesarean section.⁸⁻¹⁰

A recent study evaluated the efficacy of phenylephrine on attenuation of hypotension during induction of anaesthesia with propofol, and concluded that phenylephrine in doses of 100mcg effectively attenuates hypotension during induction with propofol.¹¹ However, the study included patients between 15-65 years with the mean age of 33-35 years old and did not focus on older patients.

The aim of this study is to determine the efficacy of phenylephrine in two different doses i.e. 100mcg and 200mcg, given during induction to counteract the anticipated hypotensive effect of propofol in older patients aged over 55 years.

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MATERIALS AND METHODS

This was a randomised controlled trial conducted in University Malaya Medical Centre (UMMC). The study was approved by the UMMC ethics committee and informed written consent was obtained from each patient.

Seventy-two ASA physical status I – II patients aged 55 years or older, scheduled for elective surgery under general anaesthesia were recruited into the study. Patients were excluded if there was a history of hypertension, angina pectoris, heart failure, cerebrovascular disease, thyrotoxicosis, or if systolic or diastolic arterial pressure at pre-operative evaluation was > 200mmHg and 110mmHg respectively.

The study drug was prepared by the investigator but both the anaesthetist administering the drug and the patient were blinded. The study drug was given together with propofol in the same syringe. Patients were randomly allocated to one of three groups of 24 patients. Group 1 received propofol mixed with 2 ml of 0.9% saline. Group 2 was given propofol mixed with 100mcg of phenylephrine (in 2 ml) and Group 3 received propofol mixed with 200mcg of phenylephrine (in 2 ml).

Patients did not receive premedication. After baseline measurements of heart rate and blood pressure, patients were pre-oxygenated for three minutes. Anaesthesia was then induced with fentanyl 1.5mcg/kg and propofol 2mg/kg. Propofol was mixed with the study drug and this was given over 15 seconds. Ventilation was assisted manually via face mask in all patients for five minutes after induction of anaesthesia. Immediately following induction, anaesthesia was maintained with oxygen/air mixture and 2% sevoflurane. Following the study period, anaesthesia continued as required for the operation.

Electrocardiography, heart rate and oxygen saturation were monitored continuously. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) (using non-invasive blood pressure monitor), and heart rate (HR) were recorded at one minute intervals for up to five minutes after the end of the propofol injection. Rescue medication with phenylephrine 100mcg was given if systolic pressure decreased to <80mmHg and atropine 0.4mg was given if heart rate decreased to <40 beats per minute (bpm) during this study period. Data from patients who required rescue medication was included. Measurements at three minutes before induction of anaesthesia served as baseline.

The SPSS 19.0 for windows was used for statistical analysis. Demographic data were compared between groups by using one way analysis of variance (one way ANOVA). Haemodynamic data was analysed by one way ANOVA for between group analysis and ANOVA for repeated measures for within group analysis. Tukey HSD was used to adjust for multiple comparisons to indicate contribution by study group pairs to the differences. Chi square test was used to compare proportions of patient that required rescue medication in each study group. Differences were considered statistically significant when the p-value was <0.05.

RESULTS

There were no significant differences between groups with respect to age, weight, gender and baseline haemodynamic data before induction of anaesthesia (Table I). No adverse events were reported during the study period; e.g. anaphylaxis, allergy, desaturation, arrhythmias, myocardial ischemia or cardiovascular collapse.

Within group analysis involved comparing each haemodynamic parameter at 1, 2, 3, 4, 5 minutes after induction with the baseline variable, within each study group.

Following induction, SBP fell significantly compared to baseline throughout the study period of 5 minutes in Group 1 (control) with mean maximal decrease from baseline of 51mmHg or 35.5% ($p<0.01$) occurring at 3 minutes. SBP also dropped significantly in Group 2 (phenylephrine 100mcg) with mean maximal decrease from baseline of 55mmHg or 35.7% ($p<0.01$) occurring at 5 minutes. In Group 3 (phenylephrine 200mcg), SBP was maintained to near baseline for the first 2 minutes in which the mean decreases were 4mmHg (2.4%) and 8mmHg (5.2%) respectively ($p>0.05$). However, SBP still decreased from 3 minutes onwards with mean maximal decrease of 48mmHg or 32% from baseline (Figure 1). Similar trends were observed in the mean differences in MAP and DBP in each study group (Figures 2 and 3).

Heart rate decreased significantly from baseline for all study groups at each time interval ($p<0.01$) except for Group 1 and Group 3 at one minute where the mean differences were 7 (8.2%) and 5 bpm (6.1%) respectively ($p>0.05$) (Figure 4).

Between group analysis

In this analysis, differences in haemodynamic parameters at each time interval were compared between each study group.

Considering SBP first, there was significant difference between Group 1 (control) and Group 2 (phenylephrine 100mcg) only at one minute with mean difference in SBP of 22mmHg, whereas mean differences between Group 1 and Group 3 (phenylephrine 200mcg) were significant at 1, 2 and 3 minutes with a mean difference of 34, 44, and 29mmHg respectively ($p<0.01$). When comparing SBP values between Group 2 and Group 3, there were also significant differences at two and three minutes (25 and 16mmHg respectively, $p<0.05$) (Figure 1). Similar trends were noted in the mean differences in MAP and DBP between groups (Figures 2 and 3). No difference was noted between groups after 3 minutes for all parameters.

It can be seen from Figure 4 that there were no significant differences in heart rate between the study groups at each time interval, except at two minutes where the difference in heart rate between Group 1 and Group 3 was 11bpm ($p<0.01$).

In the control group (Group 1), 9 out of 24 patients (38%) experienced hypotension requiring rescue medication (with phenylephrine) compared to 5 patients in Group 2 (21%) and one patient in Group 3 (4%). In Group 3, 2 out of 24 patients

Table I: Baseline patient characteristics and haemodynamic data.
Values are mean (SD)

	Group 1 propofol + saline (n=24)	Group 2 propofol + phenylephrine 100mcg (n=24)	Group 3 propofol + phenylephrine 200mcg (n=24)
Age (years)	63.5 (5.7)	61.0 (5.9)	62.4 (5.8)
Weight (kg)	56.6 (12.6)	58.7 (10.4)	62.6 (13.9)
Gender (M/F)	6/18	9/15	9/15
Baseline SBP (mmHg)	144.0 (21.8)	154.5 (20.8)	152.4 (17.6)
Baseline DBP (mmHg)	85.5 (15.3)	89.8 (12.8)	86.1 (10.5)
Baseline MAP (mmHg)	109.5 (16.5)	114.8 (13.3)	113.3 (12.2)
Baseline HR (BPM)	80.8 (11.9)	74.5 (13.6)	74.4 (13.7)

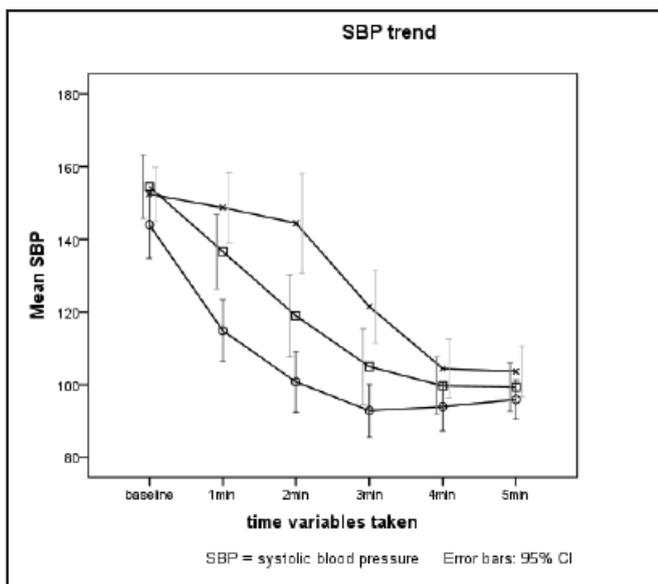


Fig. 1: Changes in SBP within and between groups. Values are in mmHg. Symbol ○ represents Group 1, □ Group 2 and × Group 3.

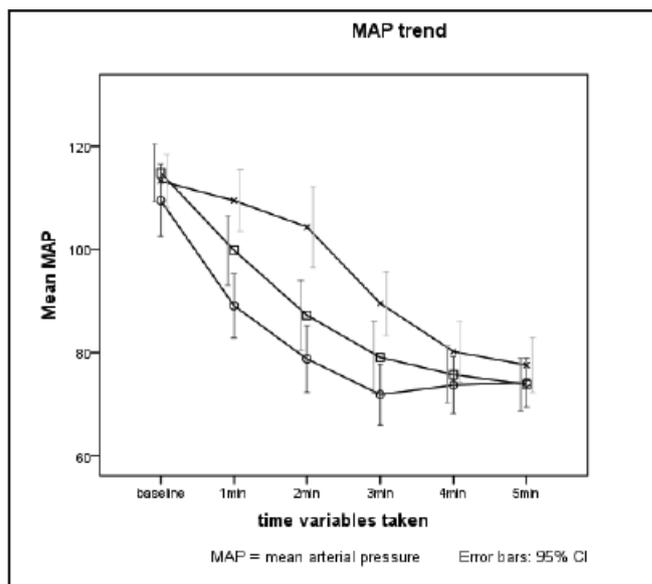


Fig. 2: Changes in MAP within and between groups. Values are in mmHg. Symbol ○ represents Group 1, □ Group 2 and × Group 3.

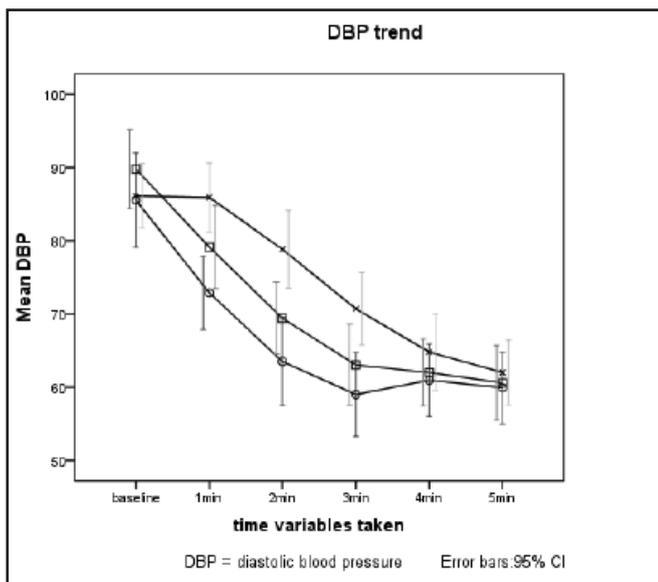


Fig. 3: Changes in DBP within and between groups. Values are in mmHg. Symbol ○ represents Group 1, □ Group 2 and × Group 3.

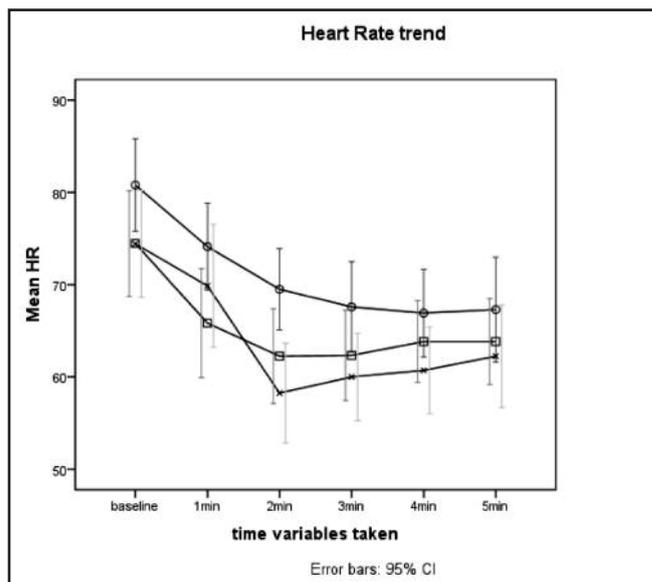


Fig. 4: Changes in heart rate within and between groups. Values are in mmHg. Symbol ○ represents Group 1, □ Group 2 and × Group 3.

(8%) required atropine due to bradycardia <40bpm. However, the differences in proportions between groups did not reach statistical significance.

DISCUSSION

Most studies have shown that a reduction in both cardiac output and systemic vascular resistance are responsible for the hypotension after induction with propofol.¹ We chose older patients (>55 years old) in this study as the hypotensive effects of propofol are detrimental to these patients. As such, they will benefit more from our study drug compared to the younger population.² Prophylactic ephedrine has been shown to attenuate the hypotensive effect of propofol in elderly patients.⁵ However, this may be accompanied by marked tachycardia with the risk of inducing myocardial ischemia.⁶ This leads to our choice of phenylephrine as a vasopressor to counteract propofol induced hypotension in the older population. Phenylephrine is a predominant alpha-1 agonist and thus a potent vasoconstrictor. After intravenous administration, it has an almost immediate onset of action with peak effect at 1-2 minutes.⁹⁻¹⁰ Hypotension due to propofol has a peak effect at 2-3 minutes after induction, which matches the peak effect of phenylephrine.

Imran *et al* conducted a recent study on patients with the mean age of 33-35 years old and concluded that phenylephrine in doses of 100mcg effectively attenuates hypotension during induction with propofol.¹¹ This dose may not be adequate for older patients. A limitation of this study was that a laryngeal mask airway was inserted for airway management during the study period, and this could have affected the hemodynamic monitoring. In our study, we assisted our patients with mask ventilation throughout the study period of five minutes, while standardising the dose of propofol, fentanyl and concentration of inhaled sevoflurane.

We observed that SBP, MAP and DBP all fell significantly after induction in the control group as expected and demonstrated in previous studies. In Group 2 using phenylephrine 100mcg, blood pressure still fell significantly from baseline although the magnitude of fall was less compared to the control group. In contrast, SBP was maintained to near baseline for the first 2 minutes after induction using phenylephrine 200mcg (Group 3), and this difference was also significant when compared to the phenylephrine 100mcg group at 2 and 3 minutes after induction. Similar trends were seen with MAP and DBP in Group 3 though to a lesser magnitude.

After 3 minutes, no statistically significant difference in blood pressure was found within and between groups. We postulate that this is due to the short duration of action of phenylephrine. Nevertheless, in clinical practice, we will usually provide some stimulation to the patient 2-3 minutes after induction, e.g. by inserting a laryngeal mask airway or direct laryngoscopy which will counteract the hypotension that persists beyond this period.

It is well known that a decrease in blood pressure induced by propofol is not accompanied by a compensatory increase in heart rate due to depression of the baroreceptor reflex and sympathetic response. The main side effect of phenylephrine

is bradycardia and thus will raise concerns especially in this context of co-administration with propofol. We observed 4% of patients in the phenylephrine 100mcg group experienced bradycardia of <40bpm requiring atropine, versus 8% of patients in the phenylephrine 200mcg group. However, the bradycardia was not associated with haemodynamic instability. Baseline heart rates in these three patients were <60bpm. Of note, heart rate fell from baseline in all groups and there were no statistically significant differences between groups.

We acknowledge that there are limitations of this study. Firstly, one would probably question the compatibility of propofol with phenylephrine and the resulting effects. Imran *et al* also mixed propofol with phenylephrine in their study but did not mention any evidence on compatibility.¹¹ There is conflicting evidence in the literature but a recent systematic review showed that phenylephrine is compatible with propofol with respect to physical and chemical stability.¹² Nevertheless, mixing propofol with phenylephrine in our study did not seem to have affected the effectiveness of each individual drug, at least not that of propofol as a hypnotic agent.

Another limitation may be that the dosage of propofol was administered according to body weight but phenylephrine was administered in two standard doses of 100mcg or 200mcg irrespective of body weight. Anaesthesia was maintained with sevoflurane 2% during the study period but this was the value on the control dial and there would certainly be inter-individual variability due to pharmacokinetic factors (e.g. wash in rate) which would affect the actual end tidal sevoflurane concentration achieved at equilibrium. These factors could have confounding effects on the haemodynamic response to propofol and phenylephrine, which might have influenced the outcome of this study.

One may also question whether attenuation of hypotension post induction is clinically relevant in terms of impact on morbidity and mortality. We did not follow up the patients after the initial study period of five minutes, and so did not study the effect of attenuating propofol induced hypotension with phenylephrine on the clinical outcome in elderly patients. A study by Reich *et al* involving 4096 patients found a statistically significant association between post-anaesthetic induction hypotension and death or morbidity in a subset of patients who underwent surgery as inpatients.¹³

CONCLUSION

Our study has shown that phenylephrine 200mcg is more effective than 100mcg in attenuating propofol induced hypotension, especially during the first two minutes after induction, in patients aged 55 years and above. There was no significant difference in heart rate trends when compared to the control group, and only a minority of patients required intervention due to bradycardia. The use of prophylactic phenylephrine at a dose of 200mcg may be considered when inducing older patients with propofol for general anaesthesia, except for those with a resting heart rate of <60 beats per minute.

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