

## ORIGINAL RESEARCH



# The Effect of Prophylactic Ephedrine on Systemic Hypotension Caused by Induction of Anaesthesia with Propofol and Sufentanil in Elderly Hypertensive Patients: A Prospective Randomized, Double-blind Placebo-controlled Clinical Trial

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## Abstract

**Objective:** To study the effectiveness of prophylactic ephedrine to prevent hypotension caused by induction of anesthesia with propofol and sufentanil in elderly hypertensive patients. **Methodology:** 70 elderly ASA grade II-III hypertensive patients undergoing elective general anesthesia were randomized into two groups to receive either intravenous ephedrine, 100 ug/kg in 5ml normal saline (Group B), or an equal volume of normal saline (Group A) before induction. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate (HR) were recorded at T0 (after entry to the operating room), T1 (1 min after induction), T2 (2 min after induction), T3 (3 min after induction), T4 (4 min after induction), T5 (when intubated), T6 (2 min after intubation), and T7 (at the start of the procedure), as well as the incidence of hypotension and bradycardia. **Results:** SBP, DBP and HR were not significantly different at T0 and were significantly different at T1 to T7 after anesthesia induction. There were statistically significant effect on hypotension and bradycardia between the two groups and group B have a lower risk of hypotension and bradycardia relative to group A. SBP and DBP decreased significantly after induction in both groups. HR decreased significantly in group A while increased in group B. **Conclusion:** Ephedrine pretreatment can minimize hypotension and bradycardia caused by propofol and sufentanil during the induction of general anesthesia in elderly patients with hypertension.

## Keywords

Ephedrine, Elderly, Hypertension, General anesthesia

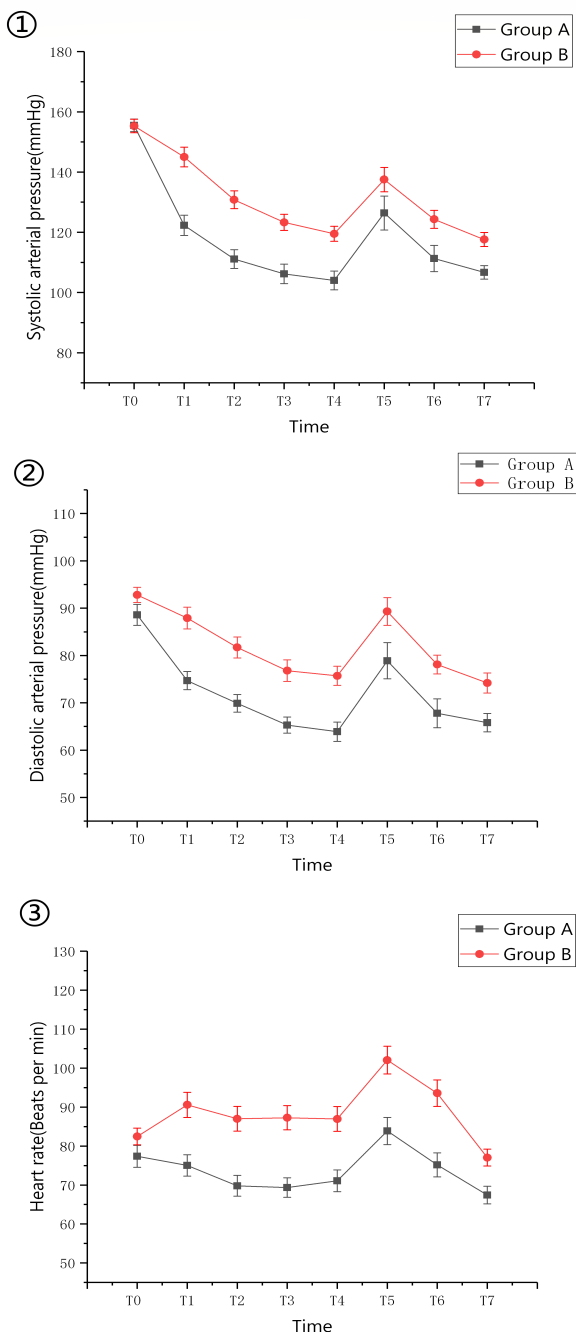
## 1. Introduction

Propofol is classified as the drug of choice for induction of anesthesia because of its rapid onset of action and complete sedation. However, anaesthesia induction with propofol is usually associated with a decrease in blood pressure and heart rate after administration of the drug [1], which is caused by the inhibition of sympathetic nerves and the dilatation of blood vessels [2, 3]. Older patients with hypertension are more susceptible to myocardial ischemia in the perioperative period due to increased secretion of catecholamines and other hemodynamic fluctuations induced by anesthesia and stimulated by tracheal intubation [4]. Sufentanil is an analgesic commonly used to suppress the response to tracheal intubation. However, sufentanil decreases heart rate, and in combination with propofol has a significant central vagal excitatory effect, increasing the incidence of bradycardia, and results in hypotension.

Ephedrine has  $\alpha$  and  $\beta$  receptor pharmacological effects,

which increases myocardial contractility and cardiac output, and increases blood pressure and heart rate [5]. Ephedrine is a moderately potent adrenergic agonist, which can directly and indirectly agonize adrenergic receptors and minimize fluctuations in blood pressure upon anesthetic induction. These mild but long-lasting effects are often used to antagonize the inhibitory effects of propofol on the sympathetic nervous system, especially during anesthetic induction [6]. However, in elderly patients with hypertension, the effect is very limited. Hypotension is more likely to occur after induction. Once the blood pressure begins to fall, even large dose of ephedrine given to patients failed to reverse the overall trend of decreasing blood pressure [7]. The results of several studies have shown that in patients receiving propofol, pretreatment with ephedrine before induction can effectively prevent hypotension and bradycardia caused by propofol [8, 9]. However, its impact on older hypertensive patients who are more likely to develop post-anesthetic induced hypotension is not known.

This study investigates the effects of pretreatment with 100



**FIGURE 1. Changes in arterial pressure and heart rate from T0 to T7 after induction of anaesthesia in patients receiving saline (A) or ephedrine (B).**

ANOVA = blood pressure and heart rate for repeated measures ANOVA with a Greenhouse-Geisser ( $\epsilon$ ) < 0.75) correction parameters for within comparison. Values are mean (SEM).

① Group A:  $df = 2.644$   $F = 41.148$   $P = 0.000$  Group B:  $df = 4.125$   $F = 35.186$   $P = 0.000$

② Group A:  $df = 3.357$   $F = 19.384$   $P = 0.000$  Group B:  $df = 3.923$   $F = 19.742$   $P = 0.000$

③ Group A:  $df = 2.740$   $F = 12.472$   $P = 0.000$  Group B:  $df = 3.580$

$F = 21.382$   $P = 0.000$

$\mu\text{g}/\text{kg}$  of ephedrine to prevent the hypotension which is associated with propofol and sufentanil induction during general anesthesia.

## 2. Methodology

### 2.1 Study population

Patients were recruited from the Department of Anesthesiology, Yongchuan Hospital, Chongqing Medical University. Patients between the ages of 65 and 90 years scheduled for elective surgery under general anesthesia; American Society of Anesthesiologists class II and III (ASA II and III); body mass index (BMI) of 18 - 28  $\text{kg}/\text{m}^2$ ; diagnosed with hypertension (classes I, II, III) were included in this study. Patients with a history of cardiorespiratory or renal disorders, those with preoperative bradycardia, tachycardia and hyperglycemia were excluded from the study.

The sample size for this study was calculated by the PASS 15.0 software as 70 patients: randomized by a computerised random number generator into 2 groups of 35 patients: placebo group A: normal saline; and group B: ephedrine. The results of grouping were placed in envelopes by data analyst. We were in the traditional way of surgical patients with preoperative visit to evaluate the patients for eligibility the day before the surgery and randomly selected an envelope if anyone qualified. When patients entered the operating room, a nurse would open the envelope and placed 30 milligrams (mg) per 5 milliliters (ml) ephedrine or 5ml saline in an unmarked 5ml syringe. The anesthesiologist and data collectors were unaware of the individual groups and content of the syringes. All consecutive eligible patients were included in the study.

### 2.2 Data collection

Preoperatively, patients received 2  $\text{ml}/(\text{kg}\cdot\text{h})$  of a 2/3 dextrose 5% - 1/3 normal saline (0.9%) infusion during an 8 hour fasting period. After the patients entered the operating room, baseline vital signs and invasive arterial blood pressure measurements were recorded. A rapid infusion of sodium chloride and polymagnetin peptide was infused at a rate of 15  $\text{ml}/\text{min}$  over 30 minutes. Patients received either intravenous 100  $\mu\text{g}/\text{kg}$  ephedrine in 5ml normal saline or an equal volume of normal saline. 3 minutes after administration of ephedrine or saline, anesthesia was induced with intravenous propofol 1.5  $\text{mg}/\text{kg}$  over 30 seconds, midazolam 0.05  $\text{mg}/\text{kg}$ , sufentanil 0.3 - 0.4  $\mu\text{g}/\text{kg}$ , and rocuronium bromide 0.6  $\text{mg}/\text{kg}$ . Fiberoptic bronchoscopy-guided endotracheal intubation was performed 5 minutes after the induction. Controlled ventilation continued with a rate of 12 breaths/min and a tidal volume of 6 - 8  $\text{ml}/\text{kg}$  aiming for an end-tidal carbon dioxide ( $\text{EtCO}_2$ ) of 35 - 40  $\text{mmHg}$ . 5 minutes after the intubation, anesthesia was maintained with 1% - 3% sevoflurane inhalation and supplemented with, sufentanil 0.2 - 0.4  $\mu\text{g}/(\text{kg}\cdot\text{h})$ , propofol 50 - 100  $\mu\text{g}/(\text{kg}\cdot\text{min})$  at the start of the procedure, and the addition of rocuronium bromide 0.03 $\text{mg}/\text{kg}$  intermittently as needed. An insulation blanket and a continuous warming device were used during surgery to maintain the patient's temperature at least 36  $^{\circ}\text{C}$  and the bispectral index (BIS) was monitored to maintain a value between 40 - 60.

**TABLE 1. Basic characteristics in patients receiving metaraminol or saline before induction of anaesthesia.**

	Group A (n = 35)	Group B (n = 35)	p-value
Age; Medians (interquartile range), years	67 (65,69)	66 (65,69)	0.720
Weight; kg	60.88 (10.8)	65.51 (10.3)	0.071
Height; cm	162 (6.0)	163 (7.1)	0.332
Gender, females: males	13 (37)/22 (63)	15(43)/20( 57)	0.403
ASA, II: III,	25(71)/10(29)	26(74)/9(26)	0.906
Grade of hypertension, 1;2;3	9(25)/25(71)/1(2)	11(32)/20(57) /4(11)	0.278

Values are mean (SD) or n (%), unless otherwise mentioned. Grade 1 hypertension: sitting systolic blood pressure  $\geq 140$  mmHg and  $< 160$  mmHg or sitting diastolic blood pressure  $\geq 90$  mmHg and  $< 99$  mmHg. Grade 2 hypertension: sitting systolic blood pressure  $\geq 160$  mmHg and  $< 180$  mmHg or sitting diastolic blood pressure  $\geq 100$  mmHg and  $< 110$  mmHg. Grade 3 hypertension: sitting systolic blood pressure  $\geq 180$  mmHg or sitting diastolic blood pressure  $\geq 110$  mmHg.

**TABLE 2. SBP, DBP and HR of patients before and after induction of anesthesia with propofol and sufentanil.**

Studied groups	Before induction		After induction				Intubation		Procedure began
	T0	T1	T2	T3	T4	T5	T6	T7	
SBP(mmHg)									
Group A	152(144,166)	122.3(20.0)	111.1(18.4)	106.2(19.1)	104.0(18.4)	118(102,147)	111.3(25.8)	106.7(13.2)	
Group B	155.3(13.2)	145.0(12.2)	130.8(17.6)	121(113,131)	119.5(14.7)	137.5(24.0)	124.3(17.8)	117.6(13.7)	
p-value	0.948*	0.000	0.000	0.000 <sup>#</sup>	0.000	0.048 <sup>#</sup>	0.018	0.001	
	DBP(mmHg)								
Group A	87(81,96)	73(66,83)	69.9(11.0)	65.3(10.0)	63.9(12.0)	78.9(22.7)	67.8(18.0)	65.8(11.4)	
Group B	92 (86,97)	87.9(13.6)	81.7(13.1)	78(70,82)	75.7(11.9)	89.3(17.3)	78.1(11.7)	74.2(12.5)	
p-value	0.131 <sup>#</sup>	0.000 <sup>#</sup>	0.000	0.000 <sup>#</sup>	0.000	0.034	0.006	0.005	
	HR(Beats per min)								
Group A	77.3(16.7)	75.0(16.3)	67(56,82)	65(56,81)	71.0(16.4)	83.8(20.5)	71(61,87)	67.4(13.3)	
Group B	82.4(12.5)	90.5(18.9)	81(72,99)	80(72,107)	83(73,105)	102.0(20.9)	93.5(20.1)	77.0(12.8)	
p-value	0.155	0.000	0.000 <sup>#</sup>	0.000 <sup>#</sup>	0.000 <sup>#</sup>	0.000	0.000 <sup>#</sup>	0.003	

Values are mean (SD) or Medians (interquartile range), Two independent samples t-test. <sup>#</sup> Mann-Whitney U test.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) at T0 (after entry into the operating room), T1 (1 min after induction), T2 (2 min after induction), T3 (3 min after induction) T4 (4 min after induction), T5 (when intubated), T6 (2 min after intubation), T7 (at the start of the procedure) was recorded as was the number of episodes of hypotension and bradycardia.

### 2.3 Statistics

The data were analyzed using SPSS (Statistical Package for Social Sciences) version 26, Descriptive summary statistics of each group were presented as mean (SD) for normally distributed and median and interquartile range for not normally distributed outcome variables and frequencies and percentages for categorical variables. The Chi-square test was used for comparison of frequencies. Two independent samples t-test was used for comparison of differences between two groups for normally distributed outcome variables, otherwise Mann-Whitney U test would be used. ANOVA for repeated measures for within group analysis. Logistic regression was used for analyzing incidences of hypotension and bradycardia. A p-value  $< 0.05$  was considered as significant.

### 3. Results

The Median age of the patients in this study was 65 (65 - 66), and there was no statistical difference in age, weight, height and basic characteristics between two groups ( $p > 0.05$ ) (Table 1).

SBP, DBP and HR of patients before and after induction of anesthesia are presented in Table 2. SBP, DBP and HR were not significantly different at T0 and were significantly different at T1 to T7 after anesthesia induction between the two groups.

Table 3 showed that hypotension occurred 2.7 times as often in group A compared with group B and bradycardia occurred 8 times as often in group A compared with group B. Logistic regression model showed group B have a lower risk of hypotension and bradycardia relative to group A.

As shown with ANOVA for repeated measurements, SBP fell significantly compared to baseline throughout the study period in Group A with mean maximal decrease from T0 of 51mmHg ( $p = 0.000$ ) occurring at T4. SBP also dropped significantly in Group B with mean maximal decrease from T0 of 37mmHg ( $p = 0.000$ ) occurring at T7. Similar trend was observed in the mean difference in DBP in each study group.

**TABLE 3. Analysis of the effect of ephedrine on the number of episodes of intraoperative hypotension and bradycardia.**

	Group A (n = 35)	Group B (n = 35)	OR ( 95% CI )	p-value
hypotension	27	10	0.117 (0.040-0.347)	0.008
bradycardia	16	2	0.071 (0.152-0.338)	0.001

*Hypotension was defined as a 30% decrease in SBP and DBP from basal values or SBP < 90 mmHg or DBP < 60 mmHg. Bradycardia was defined as HR < 60 beats per minute. ORs were adjusted for age, sex and weight.*

Heart rate decreased significantly from T0 in group A at T3, T4 and T7, where the mean differences were 7 ( $p = 0.018$ ), 8 ( $p = 0.002$ ) and 9 ( $p = 0.005$ ) bpm respectively. In contrast, heart rate increased significantly from T0 in group B at T5 and T6, where the mean differences were 19 ( $p = 0.018$ ) and 11 ( $p = 0.017$ ) bpm respectively. A detailed analysis of changes over time reveals that SBP and DBP began to fall after induction of anesthesia and then began to rise because of intubation, continuing to decline until the start of operation. HR began to decline after induction in group A, while increased in group B, then to rise when intubation, continuing to decline until the start of operation (Fig. 1).

#### 4. Discussion

Our study confirms that induction of anaesthesia with propofol and sufentanil in elderly hypertensive patients is associated with significant systemic arterial hypotension, although there was a temporary rebound of blood pressure due to stimulation of the larynx, but blood pressure was on an overall downward trend (Fig. 1). This is consistent with the observation from Hannam and others [10, 11]. Although blood pressure was also reduced in group B after induction of anaesthesia, this reduction was significantly smaller than in group A. Heart rates in the two groups were on different trends after induction, and this difference was significant. Following induction, heart rate decreased in group A with only a slight increase during intubation, which may be due to the fact that propofol alters the pressure reflex mechanism, resulting in a smaller increase in heart rates during intubation for a given decrease in arterial pressure [12]. In contrast, ephedrine increases the heart rate due to its positive inotropic effect, while offsetting and compensating for the decrease in heart rate brought about by propofol [13]. This is consistent with the result from our study, pre-treatment with ephedrine could prevent bradycardia after the induction of anaesthesia. However, this effect of preventing the heart rate from decreasing won't last long because of the effect of sevoflurane after intubation. The result of logistic regression model also showed pre-treatment with ephedrine could reduce hypotension and bradycardia incidences. On the basis of our findings, it can be concluded that a pre-induction intravenous injection of ephedrine is effective in preventing hypotension and bradycardia but does not prevent or attenuate the decrease in blood pressure and heart rate.

The antihypertensive effects of propofol are dose-dependent and increased sensitivity to propofol in the elderly, and the antihypertensive effects of propofol are also more pronounced in patients > 60 years of age [4]. The dose of propofol used to induce anesthesia in the present study is based on a study by

Dundee [14], who found that in patients > 60 years of age, an induction dose of 1.5 - 1.75 mg/kg of propofol was adequate. Although higher doses of ephedrine (0.15 mg/kg) may be more effective in preventing hypotension and bradycardia after propofol anesthesia [15], ephedrine can occasionally cause arrhythmias [16]. Therefore, it is both reasonable and safe to recommend a lower dose of the drug. Excessive increases in heart rate can increase myocardial oxygen consumption [17, 18], especially in elderly patients with hypertension, which can increase the risk of cardiovascular events [19]. Therefore, in this study we used a medium dose at induction, i.e. 100  $\mu\text{g}/\text{kg}$  of ephedrine pretreatment. Although blood pressure still trended downward, it was more moderate than group A, and less blood pressure fluctuations were associated with intubation.

Since the incidence of hypotension was too high, we could not exclude every patient from the trial because of hypotension needing vasopressor therapy. On the premise of guaranteeing safety, we did not give any vasopressor therapy to patients because of hypotension caused by induction of anaesthesia. Regarded to age and ASA status of patients, we've measured BP and HR every minute after induction of anaesthesia and before intubation to monitor haemodynamic stability, any presence of abnormal value in blood pressure or heart rate during anaesthesia induction would be excluded from the trial and immediately received therapy. An additional fluid bolus was administered prior to induction of anaesthesia to expand blood volume, which was confirmed can prevent excessive decrease in blood pressure and reduce the risk of cardiovascular accidents [20, 21]. Therefore, there was no presence of abnormal value during anaesthesia induction in our results and all consecutive eligible patients were included in the study. However, 3 patients in group A had refractory hypotension during the operation and their blood pressure returned to normal after norepinephrine administration.

Ephedrine as a vasoactive drug also has certain limitations. Compared with such powerful short-acting antihypertensive drugs as phenylephrine, the vasoconstrictor effect of ephedrine is mild. Kwok FY [22] found that phenylephrine pretreatment was effective in relieving low blood pressure caused by propofol in the first two minutes after induction, while another study shows that a continuous phenylephrine infusion can attenuate the drop in mean arterial pressure and stroke volume index during anaesthesia induction with propofol [23]. The new antihypertensive drugs, mesalamine and methoxymine, which have emerged in recent years, can also prevent hypotension. The results with mesalamine are similar to those of norepinephrine [24], while methoxymine has been shown to cause bradycardia in studies in elderly patients [25]. Despite the

disadvantages of ephedrine, it is safe in elderly hypertensive patients because of its prolonged and mild antihypertensive effect.

Some limitations of this study should be considered. We did not stratify the sample according to grade of hypertension and collect any data on chronic antihypertensive therapy in patients. Therefore, some of our outcome variables are not normally distributed because individual variability has an important impact on outcomes. Second, we did not add noninvasive cardiac output and vascular elasticity to the data collection because of limited equipment. Large elastic arteries stiffen with advancing age [26], which influences the effect of ephedrine [27]. Third, patients were treated with a standard speed of rapid rehydration before induction, but rapid rehydration loading within a short time may lead to acute pulmonary edema and heart failure [28]. For elderly hypertensive patients, goal directed therapy would be more appropriate.

## 5. Conclusions

This study indicates that ephedrine pretreatment can alleviate the hypotension and bradycardia caused by propofol during the induction of general anesthesia in elderly patients with hypertension.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

## DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

## ETHICAL APPROVAL

This study was approved by the ethical review committee of Yongchuan Affiliated Hospital of Chongqing Medical University (No 2018-38). Clinical Trial Registration: ChiCTR1800016202. All patients have signed an informed consent form.

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