

# Small dose of ephedrine for prevention of hypotension following propofol and fentanyl administration during induction of general anesthesia

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## Abstract

Induction of general anesthesia with propofol and fentanyl could result in hypotension and bradycardia. Various methods are being used to prevent these adverse effects. The aim of our study was to assess the efficacy and safety of a small dose of ephedrine in prevention of hypotension following administration of propofol

and fentanyl. This prospective, randomized, comparative study was conducted among a total of 50 patients, both genders, age 18 years up to 60 years with ASA grade I and II and some of class III, presented for elective surgery under general anesthesia. Patients were randomly allocated into one of two groups (25 patients in each): CG (the control group), which received propofol in a dose of 2 mg/kg, intravenously, over 20–30 s mixed with 2 mL normal saline; and EphG (Ephedrine group), while received propofol in a dose of 2 mg/kg, intravenously, over 20–30 s mixed with 2 mL of ephedrine (10 mg). The Mean Arterial Blood Pressure (MAP) and Heart Rate (HR) were recorded before induction and then every 1 min up to 6 min after induction. The categorical data are presented as a number and percentage and were subjected to Fisher's exact or Chi-square test for analysis. The statistical significance was  $p \leq 0.05$ . The significant differences in HR were observed in the 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> minutes with P-value, 0.018, 0.000, 0.000, respectively. However, no patient in the study participants had bradycardia. The significant differences in MAP were observed in the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> minutes with P-value, 0.035, 0.000, 0.000, and 0.000, respectively. The percentage of patient in CG who developed hypotension in the 3<sup>rd</sup> and 4<sup>th</sup> is 44% and 32% compared to 8% and 0% in EphG, with significant differences (P-value 0.004 and 0.002, respectively). Administration of small dose of ephedrine with propofol could attenuate propofol/fentanyl hypotensive and bradycardic effects.

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## Introduction

Propofol, which is an intravenous anesthetic agent, nowadays, is commonly used as an induction agent of choice during general anesthesia. It has a rapid action and rapid recovery with decreased hangover effect.<sup>1,2</sup> The problem of propofol is a sudden drop in arterial pressure. This hypotensive effect of propofol can be enhanced when combined with fentanyl even in well-rehydrated patients.<sup>2</sup> Fentanyl, which is a short-acting opioid, is a very potent analgesic and can cause hypotension and bradycardia alone. This hypotensive effect of the combination may lead to very low blood pressure and even impalpable pulse.<sup>2</sup>

In some studies, various methods are being used such as a combination of propofol with ketamine, ephedrine, atropine, glycopyrrolate, dopamine, dobutamine, and metaraminol in the prevention of this hypotension.<sup>3</sup> Ephedrine has a sympathomimetic effect resulting in the stimulation of both alpha- and beta-adrenergic receptors and also releases noradrenaline from the storage site.

Ephedrine also can be used for relaxation of bronchial smooth muscle, cardiac stimulation, and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction.<sup>4</sup> Ephedrine also causes a decrease in intestinal tone and motility, relaxation of the bladder wall, contraction of the sphincter muscle, relaxation of the detrusor muscle, and a decrease in the uterine activity.<sup>4</sup> It was hypothesized that a small dose of ephedrine, combined with propofol could decrease the hypotensive effect of propofol and fentanyl during the induction of general anesthesia. In our study, we have aimed to assess the efficacy and safety of a small dose of ephedrine in the prevention of hypotension following administration of propofol and fentanyl during induction of general anesthesia. The secondary objective was to assess propofol-fentanyl-related complications.

## Materials and Methods

This double-blind, randomized, controlled trial study was conducted in Aseer Central Hospital (ACH), Abha, KSA, from January 2017 to July 2017, following obtaining the Ethical approval from ACH Ethics and Internal Review Board (IBR) committee. Informed written consent was obtained. A total of 50 patients, both genders, age 18 years up to 60 years with ASA grade I and II and some of class III, presented for elective surgery under general anesthesia, were enrolled. Patients with a history of closed-angle glaucoma, pregnancy, pheochromocytoma, asymmetric septal hypertrophy, idiopathic hypertrophic subaortic stenosis, Monoamine Oxidase Inhibitor (MAOIs), hypersensitivity to ephedrine, contraindication to propofol, and hypotension or shocked were excluded from the study as well as patient unwilling to participate in the study.

Following preoxygenation for 3 to 5 min, induction with propofol, fentanyl, and rocuronium was carried out. Patients were randomly allocated into one of two groups (25 patients in each): CG (the control group), which received propofol in a dose of 2 mg/kg, intravenously, over 20–30 s mixed with 2 mL normal saline; and EphG (Ephedrine group), which received propofol in a dose of 2 mg/kg, intravenously, over 20–30 s mixed with 2 ml of ephedrine (10 mg). The Mean Arterial Blood Pressure (MAP) and Heart Rate (HR) were recorded before induction and then every 1 min up to 6 min after induction. Ringer's lactate solution was used for the maintenance and replacement fluids. Drugs were prepared and administered by an assigned nurse of anesthesia. Drugs were blinded from assigned anesthesia doctor and monitoring anesthesia nurse.

Recording of HR, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and mean arterial blood pressure were carried out just before induction and every minute after induction up to 6 minutes. Hypotension was defined when there was a drop-in MAP of at least 20% from the baseline. Other monitoring of the vital signs of patients was continued as usual. The primary outcome of the study was the attenuation of the hypotensive effect of propofol/fentanyl by a small dose of ephedrine. The secondary objectives were the adverse effect of ephedrine. For data entry and analysis, the Statistical Package for Social Sciences 21.0 (IBM, Armonk, New York, USA) was used. For sample size calculation, the MAP was used as the primary outcome of this study. To achieve a 2-sided type 1 error of 0.05% with a power of 80%, a total number of 50 patients, 25 in each group, would be enough. A number of 54 patients were enrolled in the study and due to the exclusion of 4 patients, 50 patients were included in the study, 25 patients in each group (Figure 1). The categorical data are present-

ed as a number and percentage and were subjected to Fisher's exact or Chi-square test for analysis. The continuous data are presented as mean and standard deviation and were subjected to student t. test for analysis. The statistical significance was considered at  $p \leq 0.05$ .

## Results

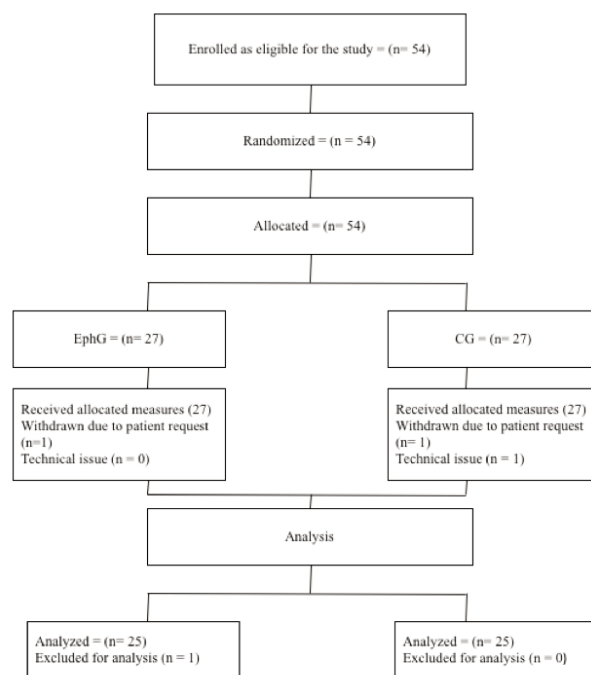
A total of 50 patients were included in this study. The demographic of the study patients, in the two groups, in respect to age, gender, weight, and ASA grade were compared with no statistical differences (Table 1).

Two groups show no differences in the base heart rate. The mean of the heart rate in CG in the first and second minutes show no difference between the two groups. The significant differences were observed in the 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> minutes with P-value, 0.18, 0.000, 0.000, respectively (Table 2). However, no patient in the study participants had bradycardia.

**Table 1. The characteristic demographic between the two groups.**

Character	CG, n=25 (%)	EphG, n=25 (%)	P-value
Age 40+4.7	39.6+5.6	0.7856	
Weight	75.32+4.3	74.86+3.9	0.6937
Gender			
Male	13 (52)	11 (44)	0.7880
Female	12 (48)	14 (66)	
ASA			
I	15 (60)	15 (60)	0.821
II	8 (32)	9 (36)	
III	2 (8)	1 (4)	

CG = Control Group. EphG = Ephedrine



**Figure 1. Diagram for sample size.**

Two groups show no differences in the base MAP. The mean of the heart rate in CG in the first minute shows no difference between the two groups. The significant differences were observed in the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> minutes with P-value, 0.035, 0.000, 0.000, and 0.000, respectively (Table 3).

No patient developed hypertension in the study groups. During the 1<sup>st</sup> minute no patient had hypotension. In the second minute 12% of patient in the CG group developed hypotension compared to zero patient in EphG with no statistical difference (P-value 0.07). The percentage of patient in CG who developed hypotension in the 3<sup>rd</sup> and 4<sup>th</sup> is 44% and 32% compared to 8% and 0% with significant differences with a p-value 0.004 and 0.002, respectively. No patient had hypotension in the 5<sup>th</sup> minute (Table 4).

## Discussion

Induction of general anesthesia using propofol and fentanyl could result in hypotension.<sup>5</sup> Propofol causes a propofol-mediated decrease in sympathetic activity, a decrease in systemic vascular resistance, and a decrease in cardiac output due to venous and arterial vasodilation, impaired baroreflex mechanism and depression of myocardial contractility.<sup>5-7</sup> Even without the presence of cardiovascular disease, the incidence of this propofol-mediated hypotension ranges from 25% to 67.5%.<sup>8-10</sup>

Ephedrine has been widely used as a premedication in anesthesia for various operations; with a well-known role in the prevention of intraoperative hypotension especially during regional anesthesia.<sup>11</sup> Many studies have concluded that the prophylactic injection of ephedrine could reduce the risk of hypotension by 14-37% when spinal anesthesia was used in pregnant patients for cesarean section.<sup>12-15</sup>

The most critical time for bradycardia and hypotension during anesthesia is immediately after induction and before tracheal intubation when the peak effect of induction drugs with minimal surgical stimulation.

In our study, the two groups show no differences in the base heart rate. The mean of the heart rate in CG in the first and second minutes show no difference between the two groups. The significant differences were observed in the 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> minutes with P-value, 0.18, 0.000, 0.000, respectively. However, no patient in the study participants had bradycardia.

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Our findings are consistent with the study of El-Tahan in showing the effect of ephedrine in preventing hypotension induced by propofol and fentanyl. They studied patients undergoing valvular surgery. Doses of 0.07, 0.1, and 0.15 mg/kg of intravenous ephedrine were used. Unlike our study, their study included patients aged over 60 years and with ASA III and IV.<sup>11</sup> This may explain the presence of significant side-effects such as tachycardia and subsequent risk of induced myocardial ischemia.<sup>11</sup>

The results of our study are also in line with the findings of Michelsen *et al.*, who studied women above 60 years of age scheduled for minor gynecological surgeries.<sup>13</sup> Ephedrine with doses of 0.1 and 0.2 mg/kg, were used 1 min before induction of anesthesia with propofol and fentanyl. They found that both doses of ephedrine had prophylactic effects against hypotension.<sup>13</sup>

However, it's important to notice that the ephedrine effect may differ with different doses and other anesthesia drugs used with it. This was concluded in many studies. These were observed in the studies by Masjedi *et al.* and Gopalakrishna *et al.*<sup>15,16</sup> Gopalakrishna *et al.* studied the effect of ephedrine on intubation and hemodynamic conditions during the rapid induction of anesthesia with propofol and rocuronium. They pre-treat their patients with doses of 0.075 mg/kg and 0.100 mg/kg. They found that those doses improved the intubating conditions during rapid tracheal intubation but were not effective in preventing the hypotension following induction of anesthesia.<sup>16</sup> Masjedi *et al.* observed the same when they used a dose of 0.070 mg/kg. However, Masjedi *et al.* found that the use of 0.15 mg/kg ephedrine, *i.e.*, was effective in controlling the hemodynamic parameters. This difference could be

**Table 2. The heart rate between the two groups.**

Character	CG (n=25)	EphG (n=25)	P-value
Base HR	82.63+8.3	84.5+7.2	0.3990
1	86.3+11.2	85.89+10.1	0.8924
2	83.3+11.6	87.06+7.9	0.1867
3	79.4+10.8	85.98+8.1	0.0186
4	74.8+9.9	85.23+9.8	0.0005
5	74.6+10.9	84.93+9.1	0.0007

CG = Control Group. EphG = Ephedrine. HR = Heart rate

**Table 3. The mean arterial pressure between the two groups.**

Character	CG (n=25)	EphG (n=25)	P-value
Base MAP	91.8+7.6	90.77+10.1	0.6855
1	87.1+2.3	88.3+5.8	0.3411
2	82.6+9.4	87.2+5.0	0.0358
3	75.4+7.3	83.7+9.0	0.0008
4	74.3+6.2	82.7+6.0	0.0001
5	76.4+7.5	87.6+6.4	0.0001

CG = Control Group. EphG = Ephedrine. MAP = Mean arterial pressure.

**Table 4. The hypertension and hypotension.**

Character	CG (n=25)	EphG (n=25)	P-value
Hypertension			
1	0	0	1.000
2	0	0	1.000
3	0	0	1.000
4	0	0	1.000
5	0	0	1.000
Hypotension			
1	0	0	10.000
2	3 (12)	0	0.0770
3	11 (44)	2 (8)	0.0041
4	8 (32)	0	0.0023
5	0	0	10.000

explained by the higher potency of remifentanyl used in Masjedi *et al.* study to cause bradycardia and hypotension in comparison with rocuronium.<sup>15</sup>

Gamlin *et al.* found that adding 15, 20, or 25 mg of ephedrine to 200 mg of propofol in a 40 ASA 3 and 4 patients over 60 years, posted for genito-urinary surgery appeared to be effective to obtund the hypotensive response to propofol administration. However, marked tachycardia associated with the use of ephedrine in combination with propofol was observed in the majority of patients leading to their recommendation not to use the ephedrine/propofol mixtures in elderly patients.<sup>17</sup>

El-Beheiry *et al.* included an ASA class I-II, aged 21-60 years patients undergoing elective outpatient surgery. The patients received pre-induction ephedrine sulphate of a dose of 0.070 mg/kg, pre-induction volume loading of 12 mL/kg Ringer's lactate, or no treatment. Rapid-sequence intubation with cricoid pressure using succinylcholine was used. Their findings showed that pre-induction administration of ephedrine sulphate is less efficacious than preoperative volume loading in maintaining hemodynamic stability during rapid-sequence induction with propofol and succinylcholine.<sup>18</sup>

Agarwal *et al.* also concluded that preoperative administration of ephedrine failed to prevent propofol-induced hypotension, but preoperative volume loading with 10mL/kg of ringer lactate successfully antagonized it.<sup>19</sup> Malla *et al.* conclude that crystalloid preloading is not efficacious in preventing hypotension compared to gelatine and ephedrine which were markedly attenuated, but does not fully abolish the decrease in blood pressure caused by induction.<sup>20</sup>

Dhungana *et al.* found that preloading with colloid (Haemaccel, 10 mL/kg intravenously over 10-15 minutes) or prior injection of sympathomimetic ephedrine (0.2 mg/kg *iv*), prior to induction of anesthesia with propofol (2.5 mg/kg *iv*) though are not fully efficacious in preventing hypotension caused by propofol induction, both decrease the incidence in a significant number of patients with heart rate less than baseline value in the colloid group.<sup>21</sup>

## Conclusions

The use of small doses of ephedrine could attenuate the propofol-fentanyl hypotensive effect during the induction of general anesthesia without tachycardia.

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