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Prophylactic Effect of Ephedrine in Reducing Hemodynamic Alterations Related to Anesthesia Induction with Propofol and Morphine: a Randomized Controlled Trial

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Abstract

Background and aim: Anesthesia induction by using propofol and morphine is associated with hypotension and bradycardia. In this randomized controlled trial, we compared the prophylactic effects of 0.1 and 0.2 mg/kg of ephedrine in reducing hemodynamic alterations related to anesthesia induction.

Methods: This is a clinical randomized controlled trial with 111 patients receiving elective surgery under general anesthesia. Patients were divided into three groups before inducing anesthesia with 2.5 mg/kg of propofol and 0.1 mg/kg of morphine: the control group (not received, n=37) , the low-dose group (0.1 mg/kg of ephedrine, n=37), and the high-dose group (0.2 mg/kg of ephedrine, n=37). Our primary objective was to compare the efficacy of 0.1 and 0.2 mg/kg of ephedrine in preventing hypotension due to anesthesia induction.

Results : The incidence of hypotension was highest in the control group (29.7%, 70.3%, 81.1%, 78.4% and 81.1% at 1, 2, 3, 4 and 5 min after anesthesia induction, respectively). and lowest in the high-dose group (0%, 0%, 2.7%, 10.8% and 13.5% at 1, 2, 3, 4 and 5 min, respectively). In the overall 5 minutes comparison after anesthesia induction, significant differences in the mean differences of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were observed between the high-dose and control groups (P<0.001, all parameters) and between the high- and low-dose groups (P<0.001 in SBP and MAP, P=0.001 in DBP). Between the low-dose and control groups, we observed only significant differences in the mean differences of SBP (P<0.001) and MAP (P=0.018). The comparison of hemodynamic data at 5 minutes after anesthesia induction also demonstrated significant differences in the mean differences of SBP, DBP and MAP between the high-dose and control groups (P<0.001, all parameters) and between the high- and low-dose groups (P=0.001 in SBP and DBP, P<0.001 in MAP). There was only a significant difference in the mean difference of SBP (P=0.010) between the low-dose and control groups. No significant difference in heart rate was observed between these three groups.

Conclusion: The hypotensive effect of anesthesia induction with propofol and morphine was eliminated by administering 0.2 mg/kg of ephedrine only. Both 0.1 and 0.2 mg/kg of ephedrine did not cause significant tachycardia at 1-5 min after anesthesia induction.

Keywords: anesthesia, ephedrine, hypotension, morphine, propofol

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Received April 27, 2022, Revised January 5, 2023, Accepted January 5, 2023

Introduction

General anesthesia induction by using propofol is common in clinical practice. It has many benefits, such as rapid onset and decrease in postoperative nausea and vomiting effects. However, it is associated with hypotension and bradycardia.[1,2] Morphine is also extensively used in inducing anesthesia, which has more hypotensive effects due to vasodilation from histamine release and sympatholytic and parasympathomimetic mechanisms.[3-5] Ephedrine is a sympathomimetic medication that increases blood pressure and heart rate by stimulating postsynaptic α and β adrenergic receptors.[6] It is widely used to treat hypotension from spinal and general anesthesia.

Several studies have demonstrated the counteractive effects of ephedrine on the hypotensive effects of propofol during anesthesia induction; nearly all studies used propofol along with fentanyl or remifentanil. Some studies reported tachycardia in patients using ephedrine. The primary objective of this study was to compare the efficacy of 0.1 and 0.2 mg/kg of ephedrine in preventing hypotension due to anesthesia induction using propofol and morphine. The secondary objective was to examine the effect of ephedrine on heart rate.

Methods

To guarantee the safety and well-being of all participants, this prospective, randomized, double-blinded controlled trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (2013) and was registered to the Thai Clinical Trials Registry. The study was performed in a tertiary care hospital from May 2021 to September 2021 after approval from the Institutional Ethics Committee, and prior to participation, all patients provided written informed consent.

In this study, 111 American Society of Anesthesiologists (ASA) class I-II patients aged between 18 and 60 years of either sex, without prohibition of positive pressure ventilation, undergoing elective surgery requiring general anesthesia were enrolled. The following were the exclusion criteria: patients with a history of hypertension, heart diseases, thyroid diseases, neurological diseases and respiratory diseases; those with renal insufficiency; those with an allergy to any drugs applied in the study; those receiving heart rate- or blood pressure-modifying drugs; those who were pregnant; those who were expected to be difficult to intubate; those with body mass index of more than 35 kg/m^2; those who are at risk of aspiration; those with initial systolic blood pressure (SBP) of more than 160 or less than 90 mmHg; and those who refused to participate in the study. Patients were discontinued from the study if the mean arterial pressure (MAP) was less than 60 mmHg more than twice, SBP was greater than 160 mmHg more than once, or heart rate was greater than 150 beats/min or less than 50 beats/min more than once, despite receiving protocol-compliant treatment . Hypotension was defined as a decrease in the mean arterial pressure more than 20 percent from baseline.[7]

Each patient was randomly allocated to one of the three groups using sealed envelopes . All patients were given 5 mL/kg of acetate ringer

injection 10 min before anesthesia induction. Initial blood pressure and heart rate were measured at a 3-min interval along with pre-oxygenation with 100% oxygen. Then, 0.1 and 0.2 mg/kg of ephedrine was administered to the patients in the low- and high-dose groups, respectively, by a nurse anesthetist. Neither pre-medication nor placebo were given to the patients in the control group . Within one minute after receiving ephedrine, anesthesia was induced by using 2.5 mg/kg of propofol, followed by 0.1 mg/kg of morphine, over 15-20 sec until loss of consciousness. All patients received bag mask ventilation with 100% oxygen. Following anesthesia induction, SBP, diastolic blood pressure (DBP), MAP and heart rate were recorded every minute for 5 min using calculated automated non-invasive blood pressure monitor by another nurse anesthetist who was blinded to the drugs administered in the study. Moreover, 200 mL of acetate ringer injection was rapidly injected through an intravenous line within 2 min if the MAP decreased more than 20% from baseline. If the MAP remained less than 80% of baseline after receiving acetate ringer injection, rescue medication with 6 mg ephedrine (if heart rate was less than 60 beats/min) or 4 µg of norepinephrine (if heart rate was more than 60 beats/min) would be administered. Then, a 0.6 mg of atropine was administered in patients with isolated bradycardia (heart rate of less than 50 beats/min).[7]

The number of patients in each group was calculated using continuous outcome variables based on a previous study[8], where the MAP of the patients who received 0.15 mg/kg of ephedrine was 80.1±15.9 mmHg and the MAP of the control group was 70.3±12.4 mmHg with a P-value of 0.05. This resulted in a sample size of 33 patients per group, 0.05 type-I error, and 80% power for the study. We increased the study population by 10% to account for the possibility of patients withdrawing from the study for any reason.

Statistical analysis was performed using Statistical Package for the Social Sciences (version 26.0; IBM Corporation, Armonk, NY, USA). Means and standard deviations were estimated for age, weight and baseline hemodynamic data. To compare proportions, the Chi-square and Fisher's exact tests were used. The independent t-test was employed to compare continuous variables between two groups. Intergroup comparisons of hemodynamic variables were performed using repeated measures analysis of variance with post hoc Scheffe. Significant differences were defined as those having *P*-value of <0.05.

Results

In this study, 111 patients were enrolled, with each group consisting of 37 patients. Three patients in the low-dose group received atropine for isolated bradycardia, but we analyzed them in the assigned group according to the principle of intention to treat. (Figure 1)

The mean age of the patients was 42.4±11.5 years in the control group, 42.1±12.1 years in the low-dose group and 41.1±12.6 years in the high-dose group. No differences in demographic data with respect to gender, age, weight, ASA physical status and baseline hemodynamic data were observed between the three groups. (Table 1)

At 1 to 5 min after anesthesia induction, hypotension incidence by proportion, defined as

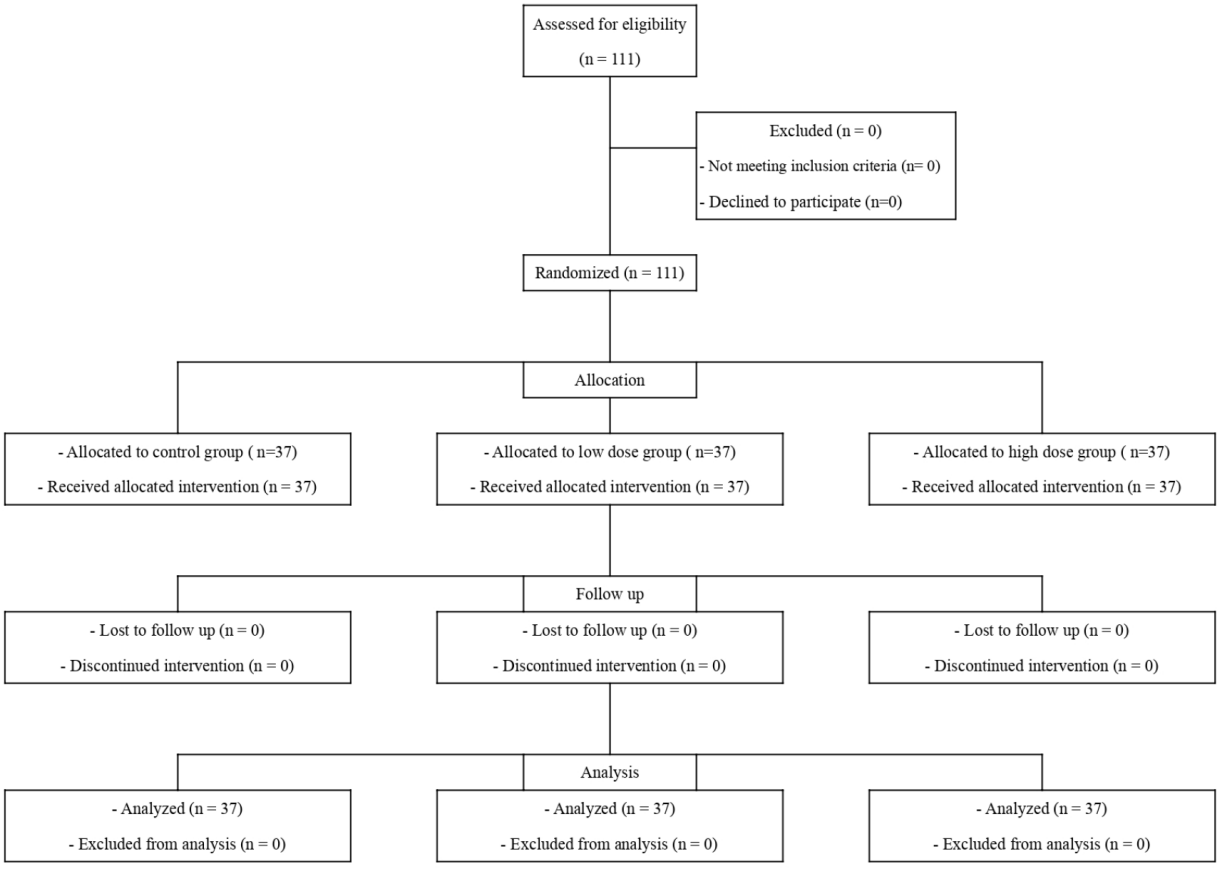


Figure 1 Consolidated standards of reporting trials diagram

the ratio of the patients with hypotension to all other patients, was highest in the control group (29.7%, 70.3%, 81.1%, 78.4% and 81.1% at 1, 2, 3, 4 and 5 min after anesthesia induction, respectively) and lowest in the high-dose group (0%, 0%, 2.7%, 10.8% and 13.5% at 1, 2, 3, 4 and 5 min, respectively). There was a significant difference in the incidence of hypotension between three groups each minute after anesthesia induction (P<0.001). (Table 2)

Figure 2 displays the SBP, DBP, and MAP values of the three groups from baseline to 1 to 5 min after anesthesia induction. Repeated measures analysis of variance with post hoc Scheffe revealed significant differences in the mean differences of SBP, DBP, and MAP obtained 1-5 min after anesthesia induction between the high-dose and control groups (P<0.001, all parameters) and between the high- and low-dose groups (P<0.001 in SBP and MAP, P=0.001 in DBP). But, between the low-dose and control groups, only significant differences in the mean differences of SBP (P<0.001) and MAP (P=0.018) were observed; no significant difference in the mean difference of DBP (P=0.139). (Table 3)

Table 1 Demographic and baseline hemodynamic parameters

	Control group (n=37)	Low-dose group (n=37)	High-dose group (n=37)	*P*
Gender (Male/Female) (n)	18/19	24/13	21/16	0.371*
Age (yr, mean±SD)	42.4±11.5	42.1±12.1	41.1±12.6	0.884†
Weight (kg, mean±SD)	59.4±10.1	62.1±11.4	59.1±10.5	0.426†
ASA PS (class I/II) (n)	29/8	6/31	29/8	0.797*
SBP (mmHg, mean±SD)	135.5±16.1	133.5±15.8	131.7±14.4	0.605‡
DBP (mmHg, mean±SD)	84.5±9.8	80.5±11.6	80.6±9.0	0.495‡
MAP (mmHg, mean±SD)	100.6±11.2	97.2±10.1	96.8±9.6	0.285‡
HR (bpm, mean±SD)	80.3±12.5	74.6±15.7	77.4±12.1	0.478‡

ASA PS = American Society of Anesthesiologists physical status; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate

*** Chi-Square test; † One-way analysis of variance; ‡ Repeated measures analysis of variance**

Significant as *P*-value <0.05

Table 2 Incidence of hypotension by proportion

	1 min			2 min			3 min			4 min			5 min		
	H/N	%	*P*	H/N	%	*P*	H/N	%	*P*	H/N	%	*P*	H/N	%	*P*
Control group	11/26	29.7	< 0.001*	26/11	70.3	< 0.001*	30/7	81.1	< 0.001*	29/8	78.4	< 0.001*	30/7	81.1	<0.001*
Low dose group	3/34	8.1		6/31	16.2		17/20	46.0		21/16	56.8		23/14	62.2	
High dose group	0/37	0		0/37	0		1/36	2.7		4/33	10.8		5/32	13.5	

H/N = hypotension/non-hypotension

Fisher's exact Test; * Significant as *P*-value < 0.05

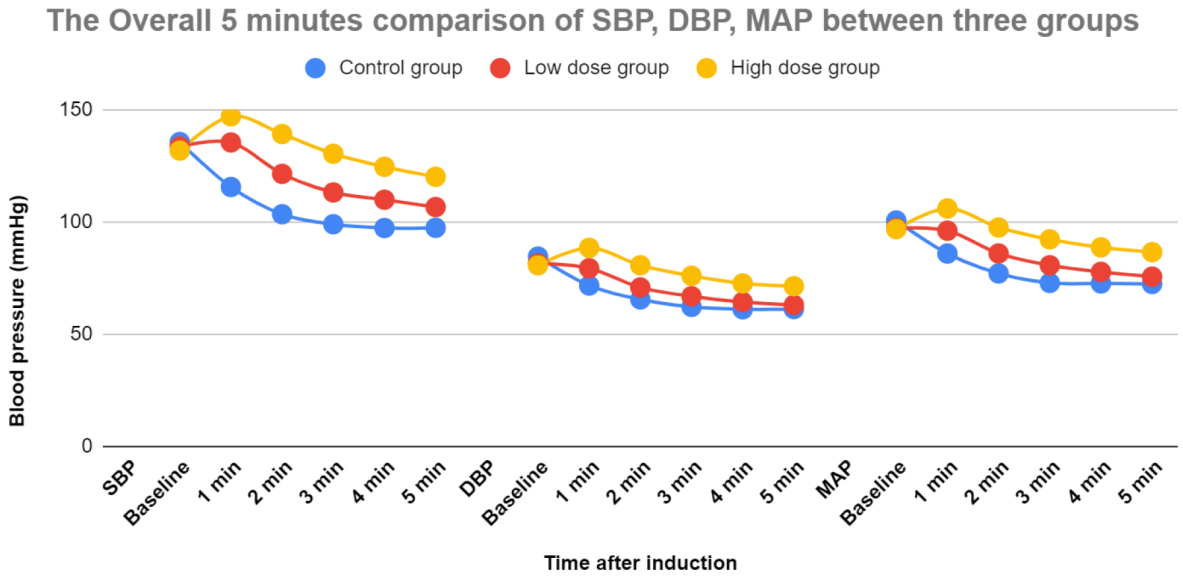


Figure 2 Overall 5-min comparison of SBP, DBP and MAP between three groups

Table 3 Overall 5-min comparison of SBP, DBP and MAP

	Mean difference of SBP (95% CI)	*P*	Mean difference of DBP (95% CI)	*P*	Mean difference of MAP (95% CI)	*P*
High dose-Control	30.8 (22.0-39.7)	<0.001*	13.5 (7.9-19.1)	<0.001*	18.0 (12.0-21.1)	<0.001*
High dose-Low dose	16.1 (7.3-24.9)	<0.001*	9.0 (3.3-14.6)	0.001*	11.0 (4.9-17.1)	<0.001*
Low dose-Control	14.7 (5.9-23.6)	<0.001*	4.6 (-1.1-10.2)	0.139	7.1 (1.0-13.1)	0.018*

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure

Repeated measures analysis of variance with post hoc Scheffe; *Significant as *P*-value < 0.05

We used the independent t-test to compare the mean differences of SBP, DBP and MAP obtained at 5 min after anesthesia induction, which corresponds to propofol's duration of action.[4] The results demonstrated that, at 5 min after induction, there were significant differences in the mean differences of SBP, DBP and MAP between the high-dose and control groups (*P*<0.001, all parameters) and between the high-dose and low-dose group (*P*=0.001 in SBP and DBP, *P*<0.001 in MAP). In contrast, between the low-dose and control groups, only a significant

difference in the mean difference of SBP was observed (*P*=0.010); there were no significant differences in the mean differences of DBP (*P*=0.455) and MAP (*P*=0.232). (Table 4)

Figure 3 depicts the heart rate from baseline to 1 to 5 min after induction of anesthesia. Intergroup comparison of heart rate between these three groups using repeated measures analysis of variance revealed no significant differences at 1-5 min after anesthesia induction (*P*=0.056).

Table 4 Comparison of SBP, DBP and MAP measured at 5 min after anesthesia induction

	Mean difference of SBP (95% CI)	*P*	Mean difference of DBP (95% CI)	*P*	Mean difference of MAP (95% CI)	*P*
High dose vs Control	22.7 (16.1-29.4)	<0.001*	10.2 (5.8-14.5)	<0.001*	14.2 (9.3-19.0)	<0.001*
High dose vs Low dose	16.2 (7.0-25.4)	0.001*	8.4 (3.4-13.3)	0.001*	11.0 (5.9-16.0)	<0.001*
Low dose vs Control	9.2 (2.3-16.2)	0.010*	1.8 (-3.0-6.6)	0.455	3.2 (-2.1-8.5)	0.232

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure
Independent t-test; *Significant as *P*-value < 0.05

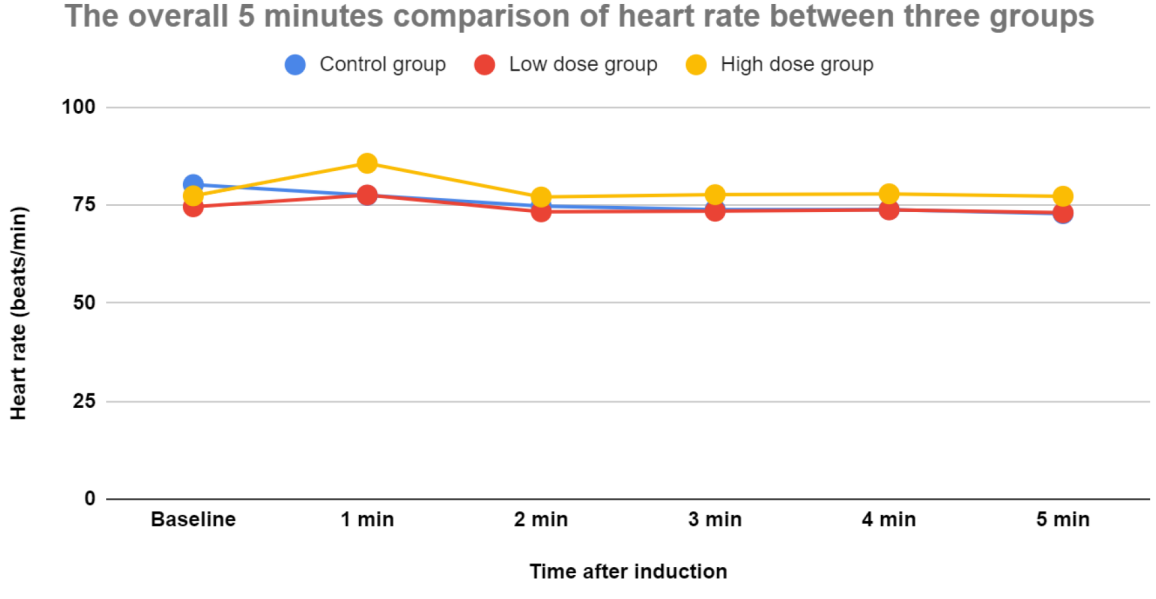


Figure 3 Overall 5-min comparison of heart rate between three groups

Discussion

The findings of this study confirmed that pre-induction with ephedrine had a beneficial effect on reducing the hypotensive effect of propofol and morphine used in inducing anesthesia. A 0.1 mg/kg of ephedrine significantly reduced but did not eradicate the reduction in blood pressure. In contrast, ephedrine at a dose of 0.2 mg/kg could abolish the hypotensive effect after anesthesia induction. Furthermore, this study did not observe a significant difference in heart rate between the groups, indicating that in healthy individuals, pre-medication with 0.1 or 0.2 mg/kg of ephedrine had no adverse effect on heart rate. The incidence of hypotension was found to be highest in the control group and lowest in the high-dose group, with significant differences among the three groups. This finding suggests that ephedrine is effective in mitigating hypotension following propofol and morphine-induced anesthesia.

Our findings corroborated those of previous studies. The study of Masjedi and coworkers concluded that 0.15 mg/kg of ephedrine might have favorable effects in preventing hypotension and bradycardia after anesthesia induction using propofol and remifentanil.[8] In this study, we used 0.2 mg/kg of ephedrine, which was slightly higher than the dose used in their study and produced the same effect without causing tachycardia. A previous study compared the prophylactic hypotensive effects of 0.2 mg/kg of ephedrine with those of crystalloid preloading during propofol- and fentanyl-induced anesthesia in healthy individuals. Their findings were comparable to those reported in this study, that 0.2 mg/kg of ephedrine has significantly attenuated but has not abolished the decrease in blood pressure after anesthesia induction and the insignificant increase in the heart rate.[9] Similarly, Dhungana and colleagues evaluated the efficacy of Haemaccel preloading versus intravenous ephedrine administration in preventing propofol-induced hypotension and have found that 0.2 mg/kg of ephedrine reduced the incidence of hypotension in healthy individuals after anesthesia induction using 2.5 mg/kg of propofol without increasing the heart rate.[10] Moreover, 0.2 mg/kg of ephedrine was slightly more effective than 0.1 mg/kg of ephedrine as prophylaxis for hypotension associated with anesthesia induction using fentanyl and propofol in elderly female patients.[11]

In contrast to our findings, Gamlin and coworkers reported full efficacy in modifying propofol's hypotensive effects when ephedrine was mixed with propofol; however, most patients experienced marked tachycardia. The difference between this study and that study could be attributed to the higher doses of ephedrine (20 and 25 mg) used in their study.[12] Additionally, a previous study also demonstrated that 0.07 and 0.1 mg/kg of ephedrine was safe and effective in countering propofol-induced hypotension during anesthesia induction during valvular surgeries. However, patients receiving 0.15 mg/kg of ephedrine had shown an increased heart rate and a greater incidence of ischemic events.[13] This finding might be because they recruited the patients with ASA class III-IV. Importantly, ephedrine could exacerbate post-intubation

hypertension and tachycardia. It was ineffective in preventing delayed hypotension and raised the heart rate.[14]

In our study, none of the patients in the high-dose group had hypotension at 1 and 2 min after the induction of anesthesia. This might be due to the rapid clinical action of ephedrine being really short, which occurs within 3 to 5 min[15,16], whereas the onset and duration of propofol are 15-45 sec and 5-10 min[4], respectively, and the onset of action of morphine is 5-10 min.[3] However, the most critical time to encounter bradycardia and hypotension due to anesthesia is immediately after induction until tracheal intubation, which normally lasts no longer than 5 min. Therefore, 0.2 mg/kg of ephedrine is an effective agent for prevention of hypotension before tracheal intubation. Hypotension is a significant issue during the anesthesia induction period. The main strength of this study is that propofol reduces blood pressure, and ephedrine is one of the alternative methods used to mitigate this effect at the first few minutes after the propofol induction.

This study had some limitations. First, it was conducted inclusively involving healthy individuals; patients with hypertension and/or other cardiovascular diseases might have different outcomes. Second, all patients were adequately hydrated before anesthesia induction. Inadequate hydration is anticipated to diminish the effects of ephedrine because it may disturb cardiovascular functions and aggravate the hypotensive effects of those anesthetic drugs. Third, patients' blood pressure and heart rate were not observed until the intubation period, whereas some studies found post-intubation hypertension and tachycardia in patients receiving pre-induction ephedrine. Therefore, we could only recommend the use of 0.2 mg/kg of ephedrine in healthy patients. Further studies with patients who have comorbidities and longer observation periods are suggested for more precise clinical recommendations.

Conclusion

Based on our findings, we concluded that 0.1 mg/kg of ephedrine did not eliminate hypotension induced by propofol and morphine during anesthesia induction. Only 0.2 mg/kg of ephedrine could eradicate the hypotensive effect. Both 0.1 and 0.2 mg/kg of ephedrine did not create significant tachycardia within 5 min after anesthesia induction. Accordingly, this study also confirmed the safety and effectiveness of 0.2 mg/kg of ephedrine as a preventive measure for propofol-induced hypotension during anesthesia induction in healthy individuals.

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