Original Article

Prophylactic effect of ephedrine to reduce hemodynamic changes associated with anesthesia induction with propofol and remifentanil

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Abstract

Background: One of the complications of anesthesia induction with propofol is a substantial decrease in arterial blood pressure and heart rate (HR), which can be intensified by adding remifentanil. This study aimed to assess the prophylactic effects of two doses of ephedrine to control the hypotension and bradycardia caused by anesthesia induced with propofol and remifentanil.
Materials and Methods: A total of 150 patients candidate for short-term minor elective orthopedic and ophthalmic surgery under general anesthesia were randomized to three groups receiving normal saline, low dose ephedrine (0.07 mg/kg) or high dose ephedrine (0.15 mg/kg). Anesthesia was induced in all groups with propofol 2.5 mg/kg and remifentanil 3 μg/kg. No neuromuscular blocking agent was used. Patients' hemodynamic status was assessed in the following four steps: Immediately before, 2 min after induction of anesthesia, as well as 1 and 5 min after intubation.
Results: A total of 143 patients consisting of 46 patients in the low dose ephedrine (0.07 mg/kg) group, 49 patients in the high dose ephedrine (0.15 mg/kg) group and 48 controls completed the trial. In all three groups, after induction of anesthesia, significant decreases occurred in the mean systolic, diastolic and mean arterial pressures, as well as in the mean HR. This decline was highest in the control group and lowest in the high dose ephedrine (0.15 mg/kg) group.
Conclusion: Our findings suggest that the administration of high dose ephedrine (0.15 mg/kg) may have a significant effect in preventing hypotension and bradycardia after anesthesia induction with propofol and remifentanil.

Key words: Adverse effects, ephedrine, hemodynamics, propofol, remifentanil

Introduction

Propofol is an intravenous short-acting hypnotic drug, which is used for induction and maintenance of general anesthesia and sedation. It has no analgesic effect and is also used in intensive care units for sedation of adult patients on mechanical ventilation and in procedures like colonoscopies.[1] Propofol is widely used in medicine because of favorable effects on the patients' recovery and low rates of associated nausea and vomiting.[1] However, the induction of anesthesia with propofol is often accompanied by a significant decrease in arterial blood pressure (BP) and heart rate (HR).[2-4]

Although a very attractive anesthetic drug, propofol has no neuromuscular blocking properties and a muscle relaxant may be needed to facilitate laryngoscopy for tracheal intubation. Recently, there has been an enthusiasm for the combined use of propofol and remifentanil to avoid the need for short acting muscle relaxants like succinylcholine.[5] This combination has also been proposed to avoid complications such as anaphylactic reaction, residual curarisation and awareness, which are sometimes seen with the use of neuromuscular blocking agents during general anesthesia.[6] Using a combination of propofol and remifentanil for anesthesia induction however, may have negative synergistic effects on patient's hemodynamic status leading to bradycardia and hypotension.[5]

The rationale behind prophylactic use of a drug to prevent hypotension and bradycardia arises from the detrimental effect of these side-effects which are often missed due to inability of the clinicians to continuously monitor hemodynamic variables in some clinical situations. Most of the anesthetic drugs used for induction of anesthesia result in a transient and rapid

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decline in BP. This further underscores the importance of preventive strategies in this setting.

As a vasopressor and sympathomimetic, ephedrine has been used safely and effectively for both prevention and treatment of anesthesia-induced hypotension especially in obstetric anesthesia.[7] It can also decrease the hemodynamic responses caused by the administration of bolus propofol.[8-10] Ephedrine has been used as a single bolus, continuous infusion or intramuscular injection.[7-9] The prophylactic use of high doses of ephedrine has demonstrated its usefulness in the treatment of propofol-induced hypotension, but it may cause marked tachycardia.[10] Prophylactic use of ephedrine has been also associated with hypertension in some clinical situations.[9] Other studies concluded that smaller doses of ephedrine prevented hypotension due to propofol induction without significant increases in HR or dysrhythmias.[11]

Since higher doses of ephedrine can cause hypertension and may endanger patients' lives, finding its optimal dose to make a balance between the effects and side-effects is crucial. This study was designed to assess the prophylactic effects of two different doses of ephedrine to prevent the hemodynamic changes caused by combined use of propofol and remifentanil for induction of anesthesia when muscle relaxation was considered as unnecessary.

Materials and Methods

This study was conducted as a randomized double-blind placebo-controlled trial. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (IRCT201112061566N3). The trial was conducted according to the Declaration of Helsinki. Informed written consent was obtained from all participants.

The eligible candidates for this trial were patients scheduled for short-term elective ophthalmic and orthopedic surgery under general anesthesia in two teaching hospitals. Patients between the ages of 20 and 50 years of American Society of Anesthesiologists class I and II (ASA I and II) and with a weight of 60-80 kg were included in this study. Those with a history of hypertension, angina, heart failure, thyrotoxicosis, reflux, cerebrovascular disease, history of using BP reducing medications, self-reported allergy to eggs and sensitivity to soy were not recruited. Patients with a history of arrhythmia and those who needed muscle relaxants during the surgery were also excluded from the trial.

A total of 150 patients were selected by convenience sampling, with its inherent bias and were assigned by unrestricted simple randomization to three groups of an equal number. Upon arrival to the operating room, standard monitoring was established including HR, BP and pulse oximetry. 5-7 ml/kg of ringer solution was administered over a period of 10 min. Patients were premedicated by one of the investigators who was blinded to the group assignment and content of the syringes. Patients randomized to the first and second groups received 0.07 mg/kg and 0.15 mg/kg ephedrine, respectively, diluted in normal saline up to 2 ml over a period of 10-15 s, respectively and the third group, considered as the control, received 2 ml normal saline. These doses were similar to the doses used by El-Tahan.[8] All three groups received similar medications for anesthesia induction consisting of 2.5 mg/kg propofol (intravenous injection using a syringe pump, 300 ml/h) and 3 μg/kg remifentanil (intravenous injection of 40 μg/ml solution over 60 s).

Hemodynamic data (HR, Mean Systolic, Mean Diastolic blood pressure) was recorded prior to induction and the second registration of hemodynamic results was performed 2 min after anesthesia induction. Then laryngoscopy and intubation was performed. For the maintenance of anesthesia, propofol (100 μg/kg/min) and remifentanil (0.1 μg/kg/min) were infused. The third and fourth measurements were recorded respectively, 1 and 5 min after the endotracheal intubation. During this 5-min interval, no surgical stimulation was performed. From then and until the end of surgery, the patient's BP was recorded as routine.

Statistical analysis

Data were analyzed using the SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). The quantitative data are presented as mean and standard deviation and the qualitative data as frequency. The Chi-square test was used for comparison of frequencies and one-way analysis of variance (ANOVA) and *post hoc* Tukey tests were used for comparison of mean values in the three groups. The statistical significance was considered as $P < 0.05$.

Results

Overall, 143 patients consisting of 46 patients in the low dose ephedrine (0.07 mg/kg) group, 49 in the high dose ephedrine (0.15 mg/kg) group and 48 controls completed the trial. Two patients from the control group and three patients from the low dose ephedrine group were excluded from the trial because of hypotension needing vasopressor therapy. One patient from each of the two groups receiving ephedrine was excluded because of tachycardia up to 150 beat/min requiring treatment with 0.2 mg bolus of propranolol for rate control.

The participants' mean age in the three studied groups was 30.2 ± 11.6 in low dose group, 29.9 ± 9.3 in high dose group and 28.1 ± 8.4 in the placebo group ($P < 0.55$).

The gender distribution was also similar among all groups ($P = 0.21$).

The systolic blood pressure (SBP) of patients is presented in Table 1. The mean SBP was not significantly different at baseline among the three groups. After anesthesia induction, the mean SBP were significantly different between three groups at 2 min after induction and 1 min after intubation ($P = 0.001$ and $P = 0.002$, respectively). The lowest mean SBP was seen in the control group and the highest in the high dose ephedrine group. The mean SBP was not significantly lower in patients who received low dose ephedrine compared with the controls at 1 min after intubation ($P = 0.11$, *post hoc* Tukey test). The mean SBP was not also significantly different among the two groups receiving ephedrine at this time ($P = 0.37$ *post hoc* Tukey test). The mean SBP was not significantly different between the groups at 5 min after intubation.

The baseline diastolic blood pressure (DBP) was not significantly different in the three groups ($P = 0.07$). After anesthesia induction, the mean DBP was significantly different between three groups ($P = 0.001$, one way ANOVA). The highest mean DBP were documented in patients receiving 0.15 mg/kg ephedrine and the least mean DBP in the control group ($P = 0.015$ Tukey test). Mean DBP was higher in patients who received low dose ephedrine compared with the controls, but it was not statistically significant ($P = 0.09$). Mean DBP were not significantly different among the two groups receiving ephedrine ($P = 0.81$). The mean DBP was not significantly different between the three groups 5 min after intubation of patients ($P = 0.146$) [Table 2].

The changes in the mean arterial BP in the three groups studied were similar to the aforementioned changes in SBP and DBP. Mean arterial pressure in patients receiving a dose of 0.15 mg/kg ephedrine were significantly higher than controls ($P = 0.017$). The mean arterial pressure was not different between the low dose ephedrine group and the controls ($P = 0.09$). The corresponding pressures were not significantly different between the two groups receiving ephedrine ($P = 0.833$) [Table 3].

As is presented in Table 4 while the mean HR was not different between the groups before induction of anesthesia ($P = 0.658$), the mean of HR was significantly different

Table 1: Systolic blood pressure (mmHg) of patients before and after induction of anesthesia with propofol and remifentanil

Time of registration	Studied groups						*P* value*
	Control		Ephedrine 0.07 mg/kg		Ephedrine 0.15 mg/kg		
	Mean	SD	Mean	SD	Mean	SD	
Before anesthesia	126.3	13.1	128.9	11.6	123.1	10.7	0.060
2 min after anesthesia	86.2	9.9	92.8	12.9	98.8	13.1	0.001
1 min after intubation	99.1	13.2	101.9	19.8	111.4	18.1	0.002
5 min after intubation	98.2	14.3	103.9	15.9	105.8	13.4	0.300

**One way ANOVA, SD = Standard deviation, ANOVA = Analysis of variance*

Table 2: Diastolic blood pressure (mmHg) of patients before and after induction of anesthesia with propofol and remifentanil

Time of investigation	Studied groups						*P* value*
	Controls		Ephedrine 0.07 mg/kg		Ephedrine 0.15 mg/kg		
	Mean	SD	Mean	SD	Mean	SD	
Before induction of anesthesia	80.4	12.1	81.4	12.5	76.2	9.4	0.070
2 min after induction of anesthesia	45.2	7.4	50.6	10.3	54.1	10.5	0.001
1 min after intubation	55.7	12.1	61.1	13.7	65.8	15.7	0.002
5 min after intubation	57.1	12.1	60.9	14.5	62.4	14.1	0.146

**One way ANOVA, SD = Standard deviation, ANOVA = Analysis of variance*

Table 3: Mean arterial blood pressure (mmHg) of patients before and after induction of anesthesia with propofol and remifentanil

Time of investigation	Studied groups						*P* value*
	Controls		0.07 mg/kg ephedrine		0.15 mg/kg ephedrine		
	Mean	SD	Mean	SD	Mean	SD	
Before induction of anesthesia	95.3	11.8	96.1	10.9	91.3	10.6	0.080
2 min after induction of anesthesia	58.1	7.6	65.3	11.7	67.8	10.4	0.001
1 min after intubation	70.3	12.4	74.5	14.1	80.1	15.9	0.005
5 min after intubation	71.6	11.9	75.4	15.2	76.5	13.5	0.179

**One way ANOVA, SD = Standard deviation, ANOVA = Analysis of variance*

Table 4: Mean heart rate (n/min) of patients before and after induction of anesthesia with propofol and remifentanil

Time of investigation	Studied groups						*P* value*
	Controls		0.07 mg/kg ephedrine		0.15 mg/kg ephedrine		
	Mean	SD	Mean	SD	Mean	SD	
Before induction of anesthesia	88.7	15.8	90.2	13.3	86.8	22.6	0.658
2 min after induction of anesthesia	68.4	10.5	73.6	10.2	77.4	13.6	0.001
1 min after intubation	73.3	13.3	77.5	13.1	82.6	17.4	0.009
5 min after intubation	71.7	12.1	76.5	13.4	79.1	16.8	0.039

**One way ANOVA, SD = Standard deviation, ANOVA = Analysis of variance*

2 min after induction of anesthesia, 1 min and 5 min after intubation between the three groups. The mean of HR was significantly higher in the high dose ephedrine group in comparison with the controls, but this was not significantly different in low dose ephedrine group compared with the control group ($P = 0.263$). The mean of HR was not significantly different between the two ephedrine groups.

Discussion

Ephedrine has been used extensively for prevention of intra operative hypotension especially during spinal anesthesia. Systematic reviews and meta-analyses have demonstrated that the prophylactic injection of ephedrine could reduce the risk of hypotension by 14-37%,[12,13] when spinal anesthesia was used in pregnant patients for cesarean section. Ephedrine has been widely used as a premedication in anesthesia for various operations;[13-15] however, a detailed literature search failed to reveal studies evaluating the prophylactic effect of ephedrine when a combination of propofol and remifentanil are used for induction of general anesthesia.

The most critical time to encounter bradycardia and hypotension during anesthesia is immediately after induction and before tracheal intubation when the peak effect of induction drugs with minimal surgical stimulation is anticipated. Thus we measured the BP and HR 2 min after induction of anesthesia (the peak effect of propofol and remifentanil). On the other hand, to examine the safety of ephedrine to prevent these side-effects, we repeated these measurement 2 and 5 min after tracheal intubation, when peak of increase in HR and BP is anticipated.

We found that the administration of ephedrine (0.15 mg/kg) may have a significant effect in preventing hemodynamic changes after anesthesia induction with propofol and remifentanil in the setting of ASA I and II ophthalmic and orthopedic surgery. However, this effect was not observed with low dose ephedrine (0.07 mg/kg). Different doses of intravenous ephedrine as low as 0.03 mg/kg up to 0.2 mg/kg have been reported to prevent hypotension during anesthesia.[5]

Our findings are consistent with the study of El-Tahan in showing the effect of ephedrine in preventing hypotension induced by propofol and fentanyl. Investigators in the study by El-Tahan used 0.07, 0.1 and 0.15 mg/kg intravenous ephedrine in patients undergoing valve surgery. However, in the latter study, significant side-effects such as tachycardia and the risk of induced myocardial ischemia were documented. Those findings may be explained by their method of patient selection because the researchers recruited patients aged over 60 years and with ASA III and IV.[8] Other reasons for the lower incidence of tachycardia in our trial may be the use of remifentanil instead of fentanyl, which can more frequently cause bradycardia.[16]

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. Ephedrine with doses of 0.1 and 0.2 mg/kg, i.e., slightly higher than the doses used in our study, were used 1 min before induction of anesthesia with propofol and fentanyl. They found that both doses of ephedrine had prophylactic effects against hypotension.[10] Substantial tachycardia was not a major problem and it was considered to be because of the effect of simultaneous use of fentanyl with propofol.

The effect of ephedrine on intubation and hemodynamic conditions in the rapid induction of anesthesia with propofol and rocuronium was evaluated in the study by Gopalakrishna *et al.*[17] They studied 100 patients with ASA I between 18 and 60 years of age and found that using ephedrine with doses of 75 μg/kg and 100 μg/kg as premedication might be associated with favorable hemodynamic condition during intubation. However, the prophylactic administration of ephedrine with the used doses was only able to reduce the arterial hypotension after induction of anesthesia, rather than eliminating it entirely. In our study, a dose of 0.07 mg/kg of ephedrine, i.e., a dose close to 75 μg/kg used in the study of Gopalakrishna *et al.*, was not effective in controlling the arterial hypotension. The dose of 0.15 mg/kg used in our study, i.e., a dose higher than the two doses used in the above study,[17] was effective in controlling the hemodynamic parameters. This difference could be explained by the higher potency of remifentanil to cause bradycardia and hypotension in comparison with rocuronium.[16] This may suggest that higher doses of ephedrine are required to prevent bradycardia and hypotension induced by propofol and remifentanil.

In reference to the side effects of ephedrine, it is suggested that ephedrine can increase BP and HR after intubation. We measured the HR and BP of the patients at 1 min and 5 min after intubation to detect any tachycardia or hypertension that could be induced by ephedrine and intubation. In our study, although there were significant differences between the three groups regarding mean systolic, and mean DBPs 1 min after intubation; however, neither parameter reached its pre-induction values. This effect of ephedrine is clinically favorable and shows its good margin of safety at one of the most vulnerable parts of anesthesia procedure to hypertension (immediately after intubation).

On the other hand, 5 min after intubation, there was no difference between the groups regarding systolic, and diastolic pressures between the control, low dose and high dose groups. This finding may suggest that ephedrine is not associated with hypertension when used in ASA I and II undergoing general anesthesia with propofol and remifentanil. The differences between HR, however, are statistically significant between the three groups at 1 and 5 min after intubation. This is in concordance with others who reported short lived increase in HR with prophylactic use of ephedrine before propofol[9,10] though this difference is not an important clinical issue (about 10 beats/min).

Some limitations of this study should be considered. First, study was conducted in healthy ASA I and II class patients with no history of cardiovascular diseases, however, patients with significant cardiovascular disease are at a higher risk. Second, all participants were hydrated adequately before induction of anesthesia, so the result could not be extrapolated to other patients with suboptimal level of intravascular volume status. Third, although dose of 0.15 mg/kg was used safely and effectively in this patient population, we could not comment on the effect of higher doses such as 0.2 mg/kg, as is used in other studies. More studies with different doses in various patients with co-morbidities are required for more precise clinical recommendations.

Hence to conclude, the findings of this trial suggest that the administration of ephedrine (0.15 mg/kg) may have favorable prophylactic effects in preventing hypotension and bradycardia after anesthesia induction with propofol and remifentanil.

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