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Effect of Ephedrine on Pain and Hemodynamic Status on Injection of Propofol

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Abstract

Background: Propofol is one of the drugs most commonly used during induction of anesthesia. The induction dose of propofol can lead to hemodynamic changes such as hypotension and bradycardia. Pain on injection is another side effect of propofol. The purpose of this study was to evaluate the effect of two different doses of ephedrine on hemodynamic status and pain on injection of propofol compared to lidocaine and placebo.

Methods: In the present study, 100 patients were enrolled. A 22 gauge cannula was inserted into the veins on the non-dominant hand of all patients. The patients were randomly allocated to 4 groups and 10 ml/kg of saline was administered over 10 minutes from each of the cannulas. Then, patients received either of these pre-treatments: 2 ml of Saline (group S); 2 ml lidocaine 2% (40 mg) (group L); Ephedrine (30 ug/kg) (group E1); or Ephedrine (70 ug/kg) (group E2). After 30 seconds all patients were administered 2.5 mg/kg of propofol with a rate of 1 ml per second. The patients were asked to give a score from 0 to 10 (0 = no pain and 10 = most severe pain) every 5 seconds until loss of consciousness. Systolic and diastolic pressures and heart rate were recorded before induction of anesthesia, before intubation, and 1, 3, and 5 minutes after intubation.

Results: Systolic, diastolic, and mean arterial pressure and heart rate following induction in E1 and E2 groups were higher than S and L groups ($P < 0.001$). There were no differences in systolic, diastolic, and mean arterial pressure and heart rate 1, 3, and 5 minutes after intubation between groups. Lidocaine and both doses of ephedrine reduced pain on injection of propofol similarly.

Conclusions: Lidocaine and high and low doses of ephedrine reduce the intensity of pain on injection of propofol. Small doses of ephedrine attenuate blood pressure and heart rate reduction after induction of anesthesia with propofol.

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Introduction

Propofol is the drug most commonly used to induce anesthesia (1). Propofol administration for induction of anesthesia can result in hemodynamic changes such as a decrease in systolic or diastolic blood pressure and also heart rate, as well as pain on injection, with an incidence of 40 to 86% (3,4). Different methods have been previously proposed to reduce the pain on injection of propofol, such as diluting the solution, injection into large veins or pre-treatment by drugs such as ondansetron, metoclopramide, or thiopental sodium (5,6). Lidocaine has also been previously suggested as a drug which may alleviate the pain on injection especially in children (7). Low dose ketamine and ephedrine have also been studied on prevention of hypotension caused by propofol induction (8,9). The aim of the present study was to determine the effect of two doses of ephedrine on prevention of injection pain and hemodynamic changes caused by propofol during induction of anesthesia.

Materials and Methods

The study protocol was approved by the Institutional Ethics Committee. An informed written consent was obtained from all the participants. In this randomized, double-blinded, placebo-controlled clinical trial, 100

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patients aged between 19 to 50 years with American Society of Anesthesiologists (ASA) physical status class I or II whom were candidates for elective laparoscopic cholecystectomy in Dr. Shariati Hospital were enrolled in the study.

Patients with a history of chronic pain, diabetes mellitus, vascular disease, and any contraindications to injection of lidocaine, propofol, or ephedrine were not enrolled in the study.

In the preoperative visit the visual analog scale (VAS) for pain (0 = no pain, 10 = most severe pain) was thoroughly explained to all the patients. No pre-medications were administered to the patients.

On arrival to the operating room, all patients were monitored with an electrocardiogram (ECG), noninvasive blood pressure, and pulse oximetry. All the required drugs were prepared in opaque syringes by an anesthetist who was not involved in either the administration of drugs to patients or patients' evaluation; thus, both the anesthesiologist and the patients were blinded to the study.

A 22 gauge cannula was inserted into the veins on the non-dominant hand of all the patients and 10 ml/kg normal saline was administered to the patients. Using a computerized program, the patients were randomly allocated into 4 groups. In group C 2 mL of Saline, in group L 2 mL lidocaine 2% (40 mg), in group E1 30 µg/kg ephedrine, and in group E2 70 µg/kg was injected to the cannula following using a tourniquet to the same arm. After 30 seconds the tourniquet was released and all the patients received 2.5 mg/kg of propofol with a rate of 1 ml per second. The patients were asked to give a score from 0 to 10 (0 = no pain and 10 = most severe pain) every 5 seconds until loss of consciousness. The highest score was recorded. Adverse effects were also recorded. Anesthesia was induced by propofol and endotracheal intubation was facilitated with 0.5 $mg.kg^{-1}$ atracurium. After tracheal intubation, anesthesia was maintained by isoflurane 1-1.5% and N2O (50%); 0.1 $mg.kg^{-1}$ atracurium and 1$\mu g.kg^{-1}$ fentanyl were administered every half hour. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7-5.3 kilo Pascal (kPA)). Systolic and diastolic pressures and heart rate were noted before induction of anesthesia, before intubation, and 1, 3, and 5 minutes following intubation.

It was estimated that a minimum of 22 patients in each group would be required in order to have a 95% power of detecting three scores in the VAS for pain, considering SD = 2.7 at a significance level of 0.05. This number was raised to 25 in each group to allow a predicted 10% drop.

Statistical analyses of the results were performed using SPSS for Windows (version 17.5, SPSS Inc., Chicago, IL, USA). The distribution of data was checked by the Kolmogorov–Smirnov test, they followed a normal distribution. The quantitative data were analyzed by one way ANOVA, post-hoc Tukey's test, and repeated measure analysis of variance. Two-tailed P value < 0.05 was considered as statistically significant.

Results

A total number of 100 patients were enrolled in the study. There was no protocol violation and none of the patients were excluded from the study. Basic characteristics of the patients including age, sex, and ASA class are presented in table 1. There was no significant difference between the groups.

There was no difference between mean systolic and diastolic pressures and heart rate recorded before induction of anesthesia in the 4 groups (Table 2). Following induction of anesthesia there were statistically significant reductions in systolic and diastolic blood pressure and heart rate in groups C and L (repeated measure analysis of variance, p = 0.002). Tukey's post-hoc test showed no difference between groups E1 and E2. Systolic and diastolic blood pressure and heart rate did not drop in measured times in any of the groups.

The VAS score for pain was less in groups L (1.6 ± 2.5), E1 (1.6 ± 2.6), and E2 (1.5 ± 2.7) than group C (4.9 ± 3.3) (P < 0.001, one way ANOVA) (Table 2). There was no significant difference in groups A, B, and C (Tukey's post-hoc test).

Discussion

In this study it was observed that lidocaine and both doses of ephedrine reduced the pain on injection of propofol. Yet, no difference was observed between groups L, E1, and E2. Moreover, both high and low doses of ephedrine prevented a decrease in the blood pressure and heart rate following induction of anesthesia. This effect was not observed by administration of lidocaine or placebo.

Table 1. Basic Characteristics of the patients

	Ephedrine 70 µg/kg	**Ephedrine 30 µg/kg**	**Lidocaine**	**Placebo**
Age (year)	33.2 ± 9	33.8 ± 3.8	32 ± 5.6	31.7 ± 4.5
Sex (Female/Male)	13/12	14/11	14/11	12/13
ASA class (I/II)	15/10	16/9	14/11	16/9
Weight (kg)	70.3 ± 9.1	72 ± 8	70.1 ± 9	68.3 ± 7.5

Data are presented as mean ± SD, ASA: American Society of Anesthesiologists

Table 2. Hemodynamic variables recorded before induction of anesthesia, and 1, 3, and 5 minutes after intubation

	Ephedrine 70 ug/kg	Ephedrine 30 ug/kg	Lidocaine	Placebo
Systolic blood pressure				
Before induction	117.32 ± 12.26	116.6 ± 12.17	117.2 ± 12.58	116.67 ± 12.6
Before intubation	106.4 ± 12/03*	102.6 ± 10.61*	82.2 ± 9.02	82.29 ± 9.32
1 min after intubation	133.2 ± 17.73	134.2 ± 14.98	127.2 ± 12.59	126.07 ± 13.35
3 min after intubation	125.4 ± 16.07	122.6 ± 13.39	112.2 ± 12.59	11.04 ± 12.16
5 min after intubation	11.2 ± 14.24	118.8 ± 11.89	106.8 ± 11.89	104.37 ± 11.54
Diastolic blood pressure				
Before induction	75.82 ± 10.16	75.8 ± 10.47	75.60 ± 10.14	76.04 ± 10.63
Before intubation	68.28 ± 8.38	65.6 ± 10.13	48.8 ± 9.38	50.79 ± 10.05
1 min after intubation	86.64 ± 12.44	86 ± 10.89	81.6 ± 11.7	83.33 ± 11.85
3 min after intubation	80.56 ± 10.56	80.6 ± 10.83	71.6 ± 9.32	63.54 ± 23.96
5 min after intubation	74.28 ± 9.83	70.8 ± 10.47	67 ± 9.57	66.66 ± 9.63
Mean arterial pressure				
Before induction	89.65 ± 10.13	89.73 ± 9.92	89.46 ± 9.93	89.58 ± 10.34
Before intubation	80.98 ± 8.61	77.93 ± 9.38	57.26 ± 8.51	59.95 ± 8.66
1 min after intubation	102.16 ± 12.71	102.06 ± 10.92	96.8 ± 10.90	97.57 ± 11.33
3 min after intubation	95.5 ± 11.02	94.6 ± 10.52	85.13 ± 9.32	79.37 ± 16.74
5 min after intubation	86.58 ± 9.92	84.46 ± 9.95	80.26 ± 9.21	79.23 ± 9.4
Heart rate				
Before induction	98.88 ± 14.35	98.28 ± 12.74	100.48 ± 12.79	98.33 ± 11.93
Before intubation	87.8 ± 13.69*	84.4 ± 12.84	54.60 ± 12.25	56.83 ± 11.46
1 min after intubation	117.24 ± 14.71	113.16 ± 14.81	110.68 ± 13.75	110.5 ± 13.71
3 min after intubation	113.92 ± 13.37	109.64 ± 14.06	106.6 ± 13.31	106.58 ± 13.23
5 min after intubation	106.36 ± 25.49	106.76 ± 13.79	103.36 ± 13.06	102.7 ± 12.63
Visual analogue scale	1.52 ± 2.7*	1.64 ± 2.62	1.56 ± 2.46*	4.87 ± 3.26

*P < 0.05; Data are presented as mean ± SD

The incidence of pain on injection of propofol is estimated to be 40 to 86.6% in adults (12,13). In a study conducted by Cheong et al. the incidence of pain was reported to be 86.6% (3).

The underlying mechanism of pain caused by injection of propofol is unknown, although the kinin cascade has been proposed as one of the probable mechanisms (14). Between different drugs proposed to reduce pain on injection of propofol, lidocaine is the most commonly used drug. Lidocaine is either injected as a bolus dose prior to propofol or is added to the propofol solution before injection; however, even patients who had received lidocaine reported an incidence of 32 to 48% pain on injection (12-14). Granisetron has also been reported to be effective in reducing pain on injection of propofol (1). The two most efficacious interventions to reduce pain on injection of propofol were use of the antecubital vein for injection, or pretreatment using lidocaine in conjunction with venous occlusion when the hand's vein was chosen (12).

Ephedrine has been previously used as a bolus dose or in combination with propofol to reduce the pain on injection (9). The mechanism by which ephedrine reduces pain is not well known. Bradykinin, as a pain modulator, inhibits norepinephrine release in the sympathetic system in the mesenteric veins and lungs in dogs. Ephedrine may decrease pain on injection of propofol by inhibiting bradykinin secretion (15).

In the present study, it was also observed that like high dose, pretreatment with low dose ephedrine not only reduces pain on injection of propofol, but also helps stabilize patients' systolic and diastolic blood pressure and heart rate following induction of anesthesia. As both low (30 ug/kg) and high doses of ephedrine (70 ug/kg) reduce pain on injection of propofol, the use of low dose is more rational. Although Cheong et al. did not report any adverse hemodynamic effects after tracheal intubation using higher doses of ephedrine (110-150 ug/kg), some adverse effects are possible in patients with cardiovascular disease. Therefore, these high doses should be used with caution in such groups of patients.

This study shows that both low (30 ug/kg) and high (70 ug/kg) dose ephedrine, injected 30 seconds before induction of anesthesia with propofol, reduce pain on injection and stabilize patients hemodynamic profile.

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