Comparison of Effects of Ephedrine, Lidocaine and Ketamine with Placebo on Injection Pain, Hypotension and Bradycardia Due to Propofol Injection: A Randomized Placebo Controlled Clinical Trial

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Abstract- Propofol is a widely used anesthetic drug because of its minor complication and also its fast effect. One of most popular complication in using this drug is pain during injection that is more sever in new generation of its components (lipid-free microemulsion). Other complications of propofol are bradycardia and hypotension. This study compares 3 drugs with placebo in control of these complications of propofol. In this double blinded randomized placebo controlled trial 140 patient who were candidates for elective surgery were divided in 4 groups (35 patients in each groups) and drugs (ephedrine, lidocaine, ketamine and NaCl solution (as placebo) were tried on each group by a blinded technician and responses to drugs were evaluated under supervision of a blinded anesthesiologist. Pain after injection, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were measured 5 times during anesthesia process of each patient. All gathered data were analyzed using t-test and Chi-square under SPSS software. Our data shows that in pain management all tested drugs can decrease pain significantly comparing with placebo (P=0.017). In control of hemodynamic parameters ephedrine could efficiently control SBP, DBP, MAP at the time 1 min after intubation. Based on our study ephedrine can be an appropriate suggestion for control of both pain and hemodynamic changes induced by propofol, although because of inconsistent result in other studies it is recommended to design a systematic review to draw a broader view on this issue.

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Introduction

Propofol is an anesthetic drug and is widely used not only by anesthesiologists but also by intensivists and emergency medicine physicians (1). Propofol has rapid onset, short duration of action and low side effects but pain during injection of propofol is a common clinical problem during anesthesia induction (2-4). There are several preparations of this agent. Long chain triglyceride propofol (LCT) is associated with more complications such as emulsion instability, need for antimicrobial agents, hyperlipidemia, pancreatitis and pain during injection (5). Other preparation is lipid-free microemulsion propofol that although has less side effects it induces more pain during injection. This type of propofol is more painful than previous preparation substantially because pain is directly related to concentration of aqueous free propofol and in this type the level of free propofol is seven times higher (6-8).

There are several studies on different pharmacologic and non-pharmacologic ways to prevent propofol injection-induced pain; such as premedication (9), icing or dilution of propofol (10,11), using concomitant drug like ketamine (12), local anesthesia (13), ondansetron (14) and opioids (15,16). Although some of these treatments can decrease extent of pain, but none of them could eliminate the pain. Also there are some other studies on using two concomitant drugs with propofol such as using lidocaine and remifentanil (17), lidocaine and dexamethasone (18) and lidocaine with metoclopramide (19).

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With increasing age, peripheral and heart vessels will be stiffen. Response of adrenergic receptors to stimulators will be weakened and autonomous system of body will fall into irregularities; then morbidity of cardiovascular diseases will increase and hemodynamic changes due to autonomic stimulations can be higher. In these patients response to propofol and other anesthetic agents can be more severe (20). Life expectancy during these years has been improved constantly and then the numbers of patients who need surgery and anesthesia is increasing (21). Hypotension during propofol injection especially in aged people is prevalent (1). This situation can be due to myocardial depression (22), sympathetic activity suppression (23) or vasodilatation (24). There are some studies on effect of ephedrine (25-27), ketamine (26) or lidocaine (27) on propofol-induced hypotension and bradycardia.

Despite the frequent studies have been done in this field, there are many contradictory and controversial results, showing the need for more studies to investigate the problem. In this study we compared the effect of three drugs (ephedrine, ketamine and lidocaine) with placebo (NaCl solution) in four separated groups on pain and hemodynamic changes induced by propofol.

Materials and Methods

This study was a double blinded placebo controlled randomized clinical trial implemented on 140 patients were chosen from candidates for first experience of elective surgery and anesthesia induction with propofol between January and May 2011 at Shahid Sadoughi Hospital, Yazd, Iran. Patients were divided into 4 groups randomly (35 patients in each group). Any patient had unpredictable complication such as bronchospasm during study, pain at the injection site before injection of study drugs or propofol, sensitivity to each of study drugs or had anxiety and lack of cooperation were excluded from study. This study is registered in Iranian Clinical Trials Registry site (IRCT.ir) as Irct ID: IRCT201102055764N1. After obtaining approval of university ethical board, complete explanation of the study method and purpose was given to patients and agreement were obtained and study was implemented. First group of patients received 0.1 mg/kg ephedrine (Sterop, Belgium) (group 1), second group received lidocaine 2% (Casppian Tamin, Iran), third received 0.1 mg/kg ketamine (Rotexmedica, Germany) and the last group received 2 ml normal saline (as control group). All drugs were administered 30 seconds before Propofol (Fresenius Kabi, Austria) injection.

Syringes of drugs were injected by an anesthesia technician who was not aware of type of injected drug and effect of drugs was also documented under supervision of an anesthesiologist who was not aware of the type of injected drug.

During slow injection of propofol, pain and its severity were assessed by a graded scale from 1 to 4. 1 (no pain), 2 (mild pain with frown), 3 (moderate pain with frown and whine) and 4 (sever pain with withdrawing of hand). Then 1.5-2 ml of fentanyl and 0.5 mg/kg atracurium were injected and after 3 minutes of ventilation patients were intubated. Heart sate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were measured 5 times (before injection of study drug, one min after injection of propofol, just before intubation, 1 min after intubation and 2 min after intubation).

Data are shown as mean±SD. All data were transferred to SPSS software and were analyzed under repeated measures, t-test and Chi-square test.

Results

Mean age of patient was 28.22±7.32. 40.7% (57 patients) of patients were female and 59.3% (83 patients) were male. The flowchart of study is shown in figure 1. Based on table 1 there was significant difference between drugs and placebo (P=0.017). Among tested drugs, ketamine had the best response but statistically there was no significant difference between drugs (P=0.76).

Table 2 shows heart rate in 4 groups of patients. Based on t-test there was no significant difference between groups in control of heart rate. Our results shows that in the age group we have done this study even in placebo group there was no sign of bradycardia (Table 2). As shown in table 2, heart rate decreased after injection of propofol and just before intubation but during later minutes it increased. This phenomenon occurred even in placebo (NaCl) group that shows a natural reaction of body probably due to vagus nerve stimulation and its parasympathetic effect.

Analysis on systolic blood pressure (SBP) changes between study groups is shown in Table 2. There was significant difference between ephedrine and other drugs in SBP at the time 1 min after intubation (P=0.025). There were no significant differences between other groups in other times.

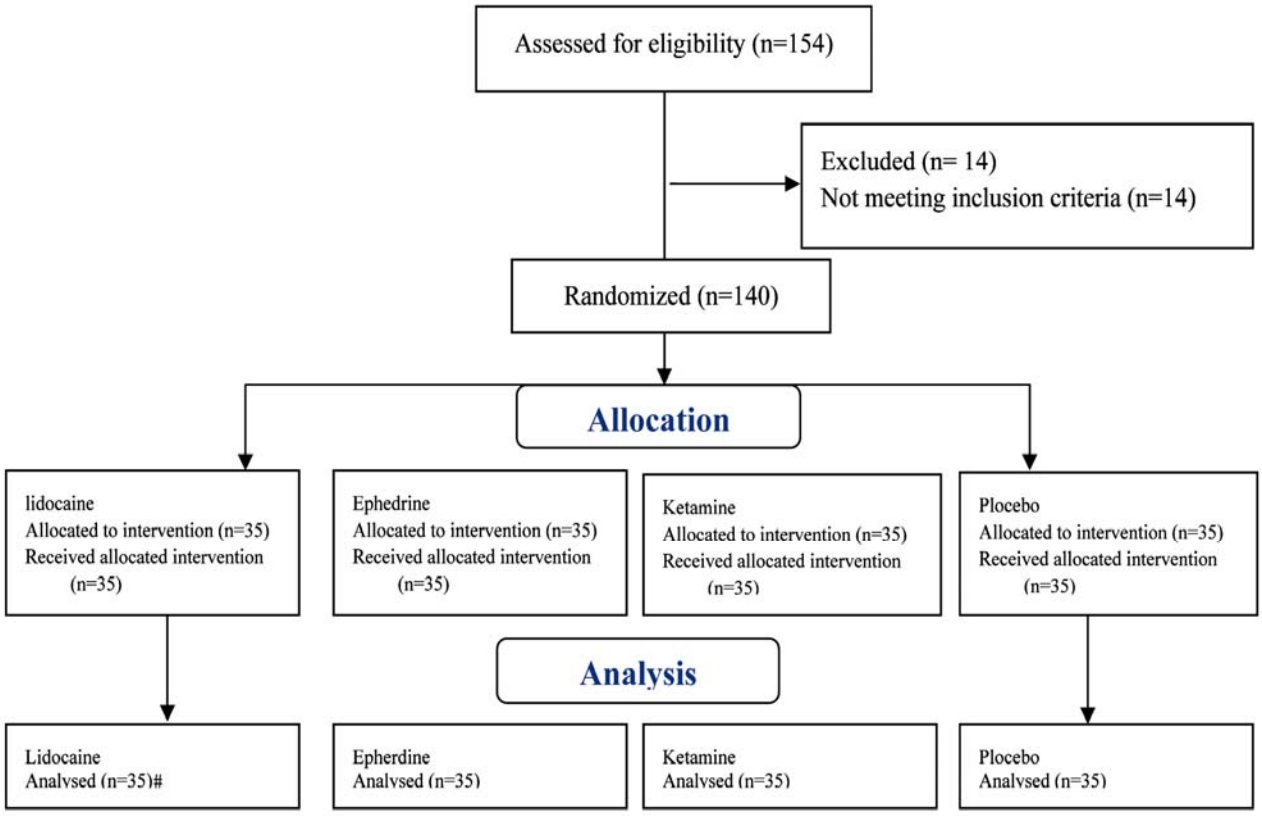

Figure 1. Flowchart of study: Comparison of effects of ephedrine, lidocaine and ketamine with placebo on injection pain, hypotention and bradycardia due to propofol injection

There was only a slight significant difference at the time just before intubation with placebo (P=0.043). Analysis of diastolic blood pressure (DBP) showed similar situation. Ephedrine had positive effect to regulate decreased blood pressure induced by propofol and intubation at the time 1 min after intubation (Table 2).

In comparison of mean arterial pressure (MAP) between groups we founded similar findings. MAP as an index reflecting both SBP and DBP can show an overall estimation about the effect of these drug groups on cardiovascular system (Table 2).

Table 1. Comparison of pain induced by propofol between the study groups. Groups: 1 (ephedrine), 2 (lidocaine), 3 (ketamine), 4 (placebo, NaCl). Pain grade scale: 1 (no pain), 2 (mild pain with frown), 3 (moderate pain with frown and whine) and 4 (sever pain with withdrawing of hand) P=0.017

			Pain grade scale				Total
			1	**2**	**3**	**4**	
Group	1	Count	21	6	4	4	35
		% within group	60.0%	17.1%	11.4%	11.4%	100.0%
	2	Count	21	8	5	1	35
		% within group	60.0%	22.9%	14.3%	2.9%	100.0%
	3	Count	26	4	3	2	35
		% within group	74.3%	11.4%	8.6%	5.7%	100.0%
	4	Count	9	12	8	6	35
		% within group	25.7%	34.3%	22.9%	17.1%	100.0%

Table 2. comparison of groups in their influence on systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR). 1 (ephedrine), 2 (lidocaine), 3 (ketamine), 4 (placebo, NaCl). *P*-values (*P*) are calculated in comparison with placebo group.

Variable	Time	Before injection of study drug	One min after injection of Propofol	Just before intubation	1 min after intubation	2 min after intubation
SBP	1	118.82±17.35	110.57±17.9	137.51±24.32	125.6±19.72	117.02±17.42
	P	0.70	0.047	0.33	0.025	0.54
	2	106.2±15.44	102.51±15.44	125.77±22.04	115.77±15.09	111.34±17.07
	P	0.65	0.42	0.29	0.89	0.75
	3	109.45±19.19	98.45±18.69	123.85±28.79	114.45±24.51	112.31±22.78
	P	0.74	0.33	0.043	0.65	0.62
	4	109.76±20.01	106.77±16.85	126.51±19.84	116.88±14.65	113.42±14.21
DBP	1	70.8±14.21	65.74±12.62	87.37±19.57	77.85±15.75	71.02±13.79
	P	0.315	0.24	0.35	0.014	0.18
	2	62.74±11.99	61.77±15.89	80.88±18.80	71.34±14.31	68.85±14.12
	P	0.17	0.27	0.72	0.25	0.65
	3	62.85±18.23	60.71±15.6	80.34±23.2	74.31±19.49	71.74±19.77
	P	0.011	0.31	0.41	0.35	0.66
	4	66.45±16.69	63.05±13.92	76.34±13.38	72.77±11.78	70.05±12.15
MAP	1	86.91±14.37	81.11±13.99	105.31±21.68	94.54±16.84	87.37±14.3
	P	0.95	0.13	0.37	0.021	0.11
	2	77.71±12.09	76.08±15.35	96.4±19.3	87.62±14.57	84.42±13.59
	P	0.64	0.31	0.56	0.67	0.81
	3	81.08±17	73.62±16.11	95.11±24.01	88.22±20.24	86.54±20.58
	P	0.45	0.33	0.14	0.91	0.96
	4	80.74±16.54	78.25±15.03	94.6±13.27	88.4±11.55	85.65±11.25
HR	1	96.51±21.43	92.25±19.2	104.74±20.36	100.91±20.79	97.45±20.83
	P	0.17	0.29	0.78	0.14	0.12
	2	96.11±14.88	92.14±19.23	102.42±17.78	98.45±16.44	96.54±15.59
	P	0.61	0.37	0.83	0.29	0.27
	3	91.08±16.31	90.31±19.2	99.02±18.11	95.51±17.12	93.25±16.51
	P	0.12	0.69	0.82	0.76	0.62
	4	92.51±17.17	91.2±18.88	97.68±19.56	93.25±20.84	92.91±19.44

Discussion

Propofol is a popular drug in anesthesiology and is widely used for induction and maintenance of anesthesia due to its good CNS absorption and short half life and also minor side effects. New generation of propofol pharmacologic formula (Lipid-free microemulsion) has fewer side effects compared with previous types but because of high concentrations of aqueous free propofol concentration, pain during injection of drug is higher than other preparations. Another complication of anesthesia induction and also propofol is hypotension and bradycardia. We compared the effect of ephedrine, lidocaine, ketamine and placebo on pain and also hemodynamic changes that occurred during propofol induced anesthesia induction.

In this study we showed that all drugs used had significant effect on controlling the pain of propofol injection in comparison with placebo. About hemodynamic change, we found that ephedrine can increase SBP, DBP and MAP at the time 1 min after intubation whereas other drugs had no detectable influence of this index comparing with placebo.

In other similar studies there are contradictory results, Cheong *et al.* (28) compared different doses of ephedrine with lidocaine and concluded that ephedrine in low dose and lidocaine can decrease the pain of propofol but have no effect on hemodynamic parameters while high doses of ephedrine can influence both pain and hemodynamic parameters. Agarwal *et al*. (29) compared the effect of ephedrine or lidocaine on pain and hemodynamic alterations following propofol

injection. They concluded that ephedrine has no effect on pain or hemodynamic parameters but lidocaine can only decrease pain. In their study, the researchers used 30 micro g/kg of ephedrine whereas we used high dose (0.1 mg/kg) of ephedrine. The different results between Agarwal *et al* study and our study can be due to this dosage difference. In another study Eren *et al.* (25) compared effect of ephedrine with placebo and concluded that ephedrine can affect pain and hemodynamic changes induced by propofol. Ozkoçak *et al.* (26) compared the effect of ephedrine and Ketamine with placebo and concluded that ketamine and ephedrine can increase blood pressure but only ketamine has positive effect to decrease pain. In this study researchers used 0.5 mg/kg of ketamine but we used 0.1 mg/kg of ketamine, it is possible that only high doses of ketamine can have an effect on hemodynamic instability induced by propofol. In another study Rokhtabnak *et al*. (27) showed that ephedrine and lidocaine have similar effects and can decrease pain after injection of propofol. Another study showed that injection of ephedrine can prevent hypotension induced by anesthesia and propofol in valve surgery (30). In another study Vosoughian *et al*. (31) concluded that using Ketamine before Propofol injection has more effect on pain and hemodynamic parameters compared with fentanyl. Another study showed that high doses of remifentanyl before propofol can lower pain but have adverse effects on blood pressure and can result in hypotension (32).

The exact mechanism of pain after propofol injection is unknown but such types of pain originates from secretion of kininogen from wall of veins and stimulation of kinin cascade (32). It seems that these contradictory results make our justifications hard. It seems that the only accepted drug for pain management is lidocaine, in almost all studies the effect of lidocaine has been accepted, but for management of hemodynamic instability there is no consensus. In our study it seems that ephedrine can be an effective drug with acceptable response for both pain management and hemodynamic control, considering with this fact that the most hemodynamic effect is needed in the first minute after intubation; because in this time the hemodynamic effects of propofol and parasympathetic effects of intubation (due to vagus nerve stimulation) are working and controlling of possible hypotension is important. But the important limitation in our study is the age group of our patients. The severe hypotension due to propofol and intubation during surgeries are more prevalent at old ages but in this study because of ethical problems and the potential possibility of life threatening situation at old ages we were obligated to do this study in a younger patients. In conclusion, we suggest ephedrine as a safe drug for decreasing the pain and increasing SBP, DBP and MAP after injection of propofol and intubation. Also considering frequent studies were held in this field there is need for a precise critical appraisal and possible Meta analysis to make an overall estimation about efficacy of each drugs used in different studies till now.

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