Original Article

Comparison of Two Drugs, Ephedrine and Dexamethasone, on Pain Caused by Propofol Injection in Patients Undergoing Elective Surgery

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ABSTRACT

Background: To relieve the pain caused by propofol injection, a wide range of medicinal and non-pharmacological methods have been investigated. The present study was conducted with the aim of comparing two drugs, ephedrine and dexamethasone, on the pain caused by propofol injection in patients undergoing elective surgery.

Methods: This double-blind randomized clinical trial study was conducted on 60 patients who were candidates for elective surgery referred to Peymaniyeh Hospital in Jahrom City. Patients were divided into two groups A: dexamethasone with a dose of 8 mg/kg and group B: ephedrine with a dose of 5 mg using a table of random numbers. Dexamethasone and ephedrine were injected within 5 seconds, and after 30 seconds, propofol 1% in the amount of 3 ml (equivalent to 30 mg) was injected into the corresponding vein at a speed of 0.5 ml per second. After the injection, the patient was clearly asked about pain or discomfort at the injection site, and the answer was yes or no, and if there was pain, its severity was recorded in the questionnaire based on verbal descriptions. The data was analyzed using SPSS Software (version 21) and using descriptive (frequency, number, standard deviation, and mean) and inferential (Chi-square test) statistics. $P<0.05$ was considered as significant.

Findings: 60 patients included in the study were divided into two groups of 30 dexamethasone and ephedrine. There was no statistically significant difference between both groups in terms of demographic characteristics (age, gender, and weight) and they were the same. Comparing the pain made by propofol injection in dexamethasone and ephedrine groups, using the Chi-square test, showed that the frequency of pain in the ephedrine group (33.3%) was not significant compared with dexamethasone group (40%) ($P=0.23$).

Conclusion: Based on the results of the present study, although more people in the ephedrine group were pain free, the amount of pain in the ephedrine and dexamethasone groups was not statistically significant.

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Introduction

In Propofol was first used in clinical practice in the early 1980s. Currently, propofol is the most widely utilized intravenous (IV) anesthetic drug for anesthesia induction, maintenance, and sedation. It is associated with the pleasant sleep induction, rapid recovery, and limited postoperative nausea, and vomiting [1]. Its profound benefits include pain during intravenous injection, occasional bradycardia, and blood pressure drop during induction. The pain caused by intravascular injection of propofol is very debilitating and this problem still persists and has never been eliminated [2-5]. The occurrence and intensity of pain during propofol injection is related to the drug's formulation [6]. To relieve pain caused by propofol, a wide range of pharmacological and non-pharmacological methods have been investigated. The addition of lidocaine to propofol, pH adjustment of propofol, injection of alfentanil, remifentanil, ketamine, metoclopramide, nafamostat, granisetron, oral clonidine, cold saline solution, ketorolac, thiopental, magnesium sulfate, ephedrine before injection, nitroglycerin use on the skin, EMLA use, or 60% lidocaine strip, propofol use at different temperatures, applying venous occlusion, adjusting the infusion rate, diluent, using different concentrations, diluting with liquid transmitters, adding long and medium chain lipids, or using wide antecubital veins can be considered as one of these medicinal approaches [7,8]. In addition, the effectiveness of propofol injection before dexamethasone injection to reduce pain has been investigated [9]. As a glucocorticoid, dexamethasone is a glucocorticoid receptor (GR) agonist and has minimal mineralocorticoid activity [10-12]. Ephiderine acts as both direct and indirect sympotomimic. This is an alpha and beta adrenergic agonist. However, it leads to the indirect release of norepinephrine from sampotic neurons, the norepinephrine inhibition, and more norepinephrine replacement is stored from vesicles [13,14]. Therefore, based on the mentioned cases and the expansion of the underlying treatments to relief pain in propofol injection site, the present study was conducted to compare the effect of ephedrine and dexamethasone on pain due to propofol injection in patients undergoing the elective surgery.

Method

This double-blind randomized clinical trial study was done on all patients undergoing the elective surgery, who referred to Peymanieh Hospital of Jahrom City in 2021 selected based on random sampling method and block randomization was carried out using the random numbers table. The inclusion criteria for the study includes class ASA I and II, the age range of 15-65 years old, and also the exclusion criteria includes the sensitivity to propofol and dexamethasone, no cooperation, disability to communicate with the research team, have some background diseases, including diabetes, sensitivity to egg and soybean, hypertension, liver and cardiovascular disorders, addiction to drug and alcohol, chronic pain syndromes, thrombophlebitis, and hysteric patients who have received phenytoin. After consent and approval of the Ethic Committee of Jahrom Medical University (IR.JUMS.REC.1399.103), in anesthesia visit before surgery, the patients were justified concerning the present study and the way to react to the pain severity of intravenous injection based on the oral scoring of pain. The scoring method for the patients' oral descriptions to the pain severity was as follow:

No pain = zero, low pain sensation = one (only when asked about pain the person expresses the presence of pain without any behavioral response), moderate pain sensation = two (when the person is asked about pain, it can express the presence of pain along with a behavioral response or declaring pain without asking), feeling severe pain = three (severe verbal response or change in facial expression, arm pulling, or shedding of tears) [15]. To select patients who are candidates for surgery participated in the study, the nurse in charge of admission completely randomly took out a card for each patient from a box containing cards named as A and B, and based on block randomization, the patient entered the study included groups A: dexamethasone with a dose of 8 mg and group B: ephedrine with a dose of 5

mg/kg. After entering the operating room and patient's placement, a peripheral vein with an angioket (no. 20) on the back of the hand (preferably the non-dominant hand) and giving the required volume with Ringer's serum (300 cc), non-invasive blood pressure monitoring, and electrocardiogram, saturation arterial blood oxygen was implanted for all patients. The studied drugs were diluted with saline in equal volumes until reaching 5 ml by the anesthesia technician at room temperature, and the name of the desired group was written as A and B on each syringe as a label. Then, according to the groups, the desired drug was injected by an anesthesiologist who was informed about the type of drug (so that he could treat it in case of any kind of complication) within 5 seconds, and after 30 seconds, propofol 1% (3 ml) (equivalent to 30 mg) made in India (Teda Company) was injected into the corresponding vein at a speed of 0.5 ml per second. After the end of the injection, the anesthesiologist, who did not know the type of injected drug, clearly asked the patient about pain or discomfort at the injection site, and the answer was clearly yes or no, and if there was pain, its intensity was based on verbal descriptions. It was recorded in the questionnaire. Then, anesthesia was continued with propofol at the rate of 2 mg per kilogram, masking, and ventilation of the lungs was further carried out, and if needed, the inhalation anesthetics or the other drugs were used. Data was analyzed using SPSS Software (version 21) and using descriptive (frequency, number, standard deviation, and mean) and inferential (Chi-square test) statistics. $P<0.05$ was considered as significant.

Ethical Considerations

This study with code no. (IR.JUMS.REC.1399.103) was approved by the Ethics Committee of Jahrom University of Medical Sciences. All participants were assured of data confidentiality and they had the right to withdraw from the study at any stage. In this study, sampling was done with the informed consent of patients and healthy people. Conducting this plan did not impose any financial costs on the patient. Hence, there was no problem in terms of medical ethics considerations.

Results

60 patients undergoing elective surgery in dexamethasone (30 people) and ephedrine (30 people) groups participated in the study. 53.3% of patients in dexamethasone group and 60% of patients in ephedrine group were males. In the dexamethasone group, the age group was 51-65 years old, and in the ephedrine group, the age group was 21-30 years old. In the dexamethasone group, the weight range was 70-80 kg, and in the ephedrine group, the weight range was more than 80 kg. However, the results of the statistical analysis with the Chi-square test showed that the dexamethasone and ephedrine groups were similar in terms of age, gender, and weight, as presented in Table 1.

Table 1 Frequency of demographic variables in patients undergoing the elective surgery who received ephedrine and dexamethasone

		Dexamethasone		Ephedrine		statistic	P-value
		N	%	N	%		
Age	≥ 20	4	13.3	4	13.3	5.92	0.21
	21-30	4	13.3	9	30.0		
	31-40	5	16.7	8	26.7		
	41-50	7	23.3	2	6.7		
	51-65	10	33.3	7	23.3		
Weight	<70	6	20.0	3	10.0		
	70-80	17	56.7	13	43.3	3.87	0.15
	Over 80	7	23.3	14	46.7		
Gender	Male	16	53.3	18	60.0	0.27	0.60
	Female	14	46.7	12	40.0		

The comparison of pain due to propofol injection in ephedrine and dexamethasone, using Chi-square test indicated that the frequency of pain in ephedrine group (33.3%) was not meaningful compared with dexamethasone group (40%) (p=0.23). In ephedrine, 26.6% and 6.7% of patients, experienced the mild and moderate pain, respectively, and it had a negative severe pain frequency. However, in dexamethasone group, 40% of patients experienced the mild pain and it had a negative moderate and severe pain (see Table 2 and Figure 1).

Table 2 Comparison of pain made by propofol injection between ephedrine and dexamethasone in patients undergoing elective surgery

		Dexamethasone		Ephedrine		Statistic	P-value
		N	%	N	%		
The pain of propofol injection	No pain	18	60.0	20	66.7	2.90	0.23
	Mild pain	12	40.0	8	26.6		
	Moderate pain	0	0.0	2	6.7		
	Severe pain	0	0.0	0	0.0		

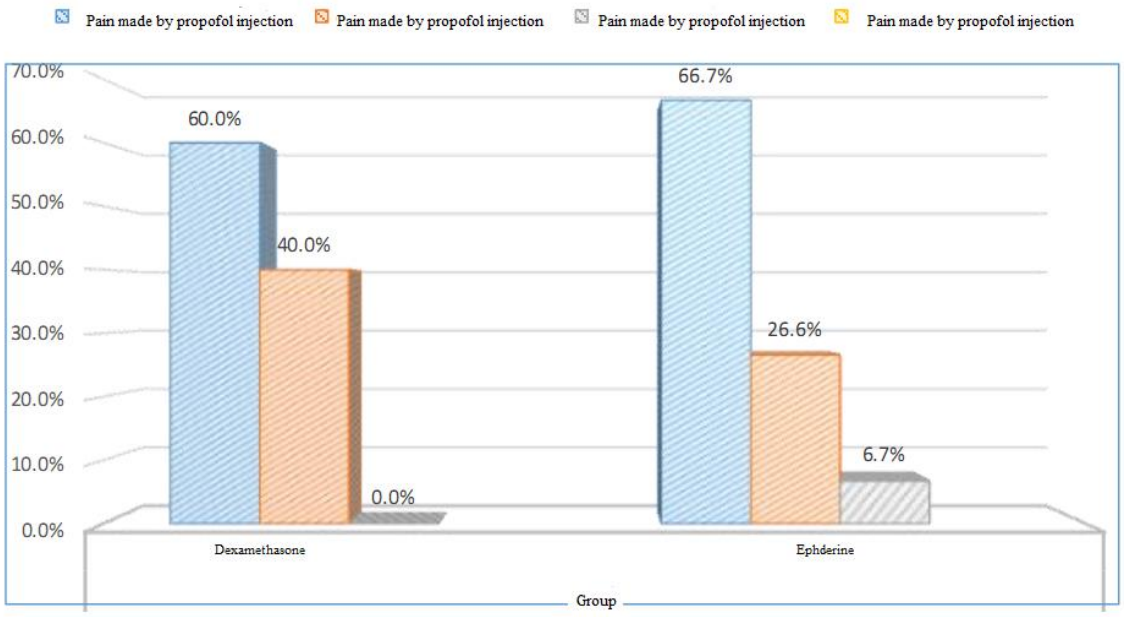

Figure 1 Comparison of pain of propofol injection between ephedrine and dexamethasone in patients undergoing elective surgery

Discussion

Various preventive treatments were introduced to relive pain during the propofol injection. The most commonly used drug is lidocaine, which reduces pain by 20-30% [16, 17]. The proposed research was conducted which aimed to compare two drugs, ephedrine and dexamethasone, on the pain caused by propofol injection in patients undergoing elective surgery. 60 patients undergoing elective surgery in dexamethasone (30 people) and ephedrine (30 people) groups participated in the study. Dexamethasone and ephedrine groups were similar in terms of demographic characteristics. Compared the pain caused by propofol injection in the dexamethasone and ephedrine groups, using the Chi-square test, indicated that the pain frequency in the ephedrine group (33.3%) compared with the dexamethasone group (40%) was not significant (p=0.23). In the ephedrine group,

26.6% and 6.7% of the patients experienced mild and moderate pain, respectively, and the frequency of severe pain was negative, while in the dexamethasone group, 40% of the patients experienced mild and moderate pain frequency that was extremely negative. Ahmed *et al.* (2013) conducted a study on the effect of intravenous dexamethasone and lidocaine on propofol-induced vascular pain and demonstrated that the incidence of moderate to severe pain was significantly reduced after propofol injection with lidocaine and dexamethasone [18]. Avrojit *et al.* (2019) compared two drugs, lidocaine and dexamethasone, in the pain prevention caused by propofol injection. According to the reported results, the intravenous dexamethasone can effectively decrease propofol-induced vascular pain. However, there is no significant difference between lidocaine and dexamethasone in declining vascular pain caused by propofol [19]. Soomro *et al.* (2021) compared the effect of lignocaine, dexamethasone, pethidine, and placebo in the prevention of pain caused by propofol injection in a randomized study. Drugs such as lignocaine, dexamethasone, and pethidine reduced the pain caused by propofol injection compared with placebo. There was no significant difference in the pain score in these three medication groups [20]. Adinehmehr *et al.* (2018) compared the effect of granistrone and dexamethasone on intravenous propofol injection pain. The pain incidence after propofol injection with granisetron and dexamethasone was significantly declined (50.7% and 49.4%) [21]. These studies are consistent with the results of the proposed study. In the current study, although dexamethasone significantly reduced the pain caused by propofol injection, there was no significant difference with ephedrine in this study. In fact, propofol releases nitric oxide (NO) from the vessels of animal and human models and causes pain in the vessel [22-24]. Based on the available evidence, corticosteroids such as dexamethasone reduce the production of nitric oxide [25, 26], and thereby, it reduces the pain of propofol injection. In their study, Ayatollahi *et al.* (2012) compared the effect of ephedrine, lidocaine, and ketamine with placebo on injection pain, hypotension and bradycardia caused by propofol injection. Based on the results reported in the pain management, all tested drugs could significantly relieve pain compared with the placebo group (P=0.017) [27]. Burman *et al.* (2019) investigated the analgesic effect of ephedrine versus lignocaine during propofol injection. Comparison of pain reduction after propofol injection in lignocaine and ephedrine group was similar (p= 0.261) [28] which is consistent with the results of the proposed study.

In the present study, although ephedrine significantly declined the injection pain, it had no significant difference with dexamethasone. Ephedrine is a vasopressor drug and is an alpha and beta adrenergic receptor agonist and works by releasing norepinephrine from sympathetic nerves and endothelium [29]. Therefore, it causes a significant amount of initial dilatation of the vessel and excessive permeability leading to a delay in the contact between propofol and free nerve ends. Ephedrine reduces the release of Bradykinin from the end of the sympathetic nerve from the endothelium and leads to a reduction in pain [30,31]. The present study revealed that the use of ephedrine at a dose of 70 mg/kg can reduce the pain caused by propofol injection.

Conclusion

In the present study, both ephiderine and dexamethasone significantly relived the pain made by propofol injection. However, the comparison of this difference was no meaningful between both groups. Therefore, the better effectiveness of both drugs can be compared using the higher dose of both mentioned medicines.

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Authors' contributions

All authors contributed toward data analysis, drafting, and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of interest

There are no conflicts of interest in this study.

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