RESEARCH ARTICLE

Comparing the Injection Pain of Propofol Emulsion 1% (MCT/LCT) and Propofol Emulsion 2% (Propofol Lipuro) in Combination with Lidocaine in Patients Undergoing Gynecologic Surgery with General Anesthesia

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Background: Propofol causes a high incidence of pain during intravenous injection. The aim of this study was to compare incidence and severity of injection pain following the administration of two different formulations of Propofol with and without 10mg Lidocaine in female patients.

Methods: One hundred ASA (American Society of Anesthesiologists) grade I and II patients, planned to undergo gynecologic surgery under general anesthesia, were included in four groups of 25 in a prospectively, randomized and double-blind study. Group A received Propofol 1%+10mg lidocaine (1cc of lidocaine1%), Group B received Propofol 1%+ 1cc preservative-free saline, Group C received Lipuropropofol +10mg lidocaine (1cc of lidocaine1%) and Group D received Lipuropropofol+1cc preservative-free saline. Injection pain was assessed using the McCrirrick and Hunter scale.

Results: No differences were found in the mean age, weight and given dose of propofol administered between all groups (P>0.05). Comparison of groups revealed significant difference in pain scores between groups (mean pain scores, GroupA:2.84 ± 0.850 vs. GroupB:3.16 ± 0.800 vs. GroupC:1.8±0.866 vs. GroupD:2.12±0.833 points).

Conclusion: The highest pain scores were found in the propofol1% without lidocaine use while lipuropropofol plus lidocaine had the lowest pain scores. We recommend premixing 10 mg of lidocaine to Lipuropropofolfor preventing or mitigation of propofol injection pain compared to Lipuropropofol alone or propofol1% with lidocaine.

Keywords: propofol; lipuro; injection pain; lidocaine

Propofol is one of the most commonly used intravenous drugs for anesthesia [1]. It is an alkyl-phenol created as fat emulsion and its effect is speedy both in the start and at the end. Context-sensitive half-life of propofol infusion in less than 3 hours is about ten minutes up to 8 hours after infusion, it is less than 40 minutes. The mechanism of action is thought to be by enhancing chloride currents activated by gamma-aminobutyric acid (GABA). In therapeutic doses, propofol lowers the ventilation effect. Moreover, due to decreased cardiac output and systemic vascular resistance, propofol causes initial reduction in blood pressure in a dose-dependent manner. The advantages of using this drug include calm induction, pleasant sleep, rapid recovery and low incidence of nausea and vomiting. [2].

Induction dose is 1-2mg/kg with infusion of 100-200µg/kg/min to maintain anesthesia [3].

Induction of anesthesia with propofol has various side effects, including injection pain, myoclonus, apnea, hypotension and rarely thrombophlebitis in the vein. One of its major problems is the injection pain. Propofol injection pain is less or equal to etomidate, equal to methohexital and more than thiopental [3]. The prevalence of propofol injection pain is reported to be 28-90 percent [4-6].

This pain is explained as stimulation of vascular endothelium, osmolarity difference, nonphysiological pH and activation of pain mediators [7].

Various methods are used to reduce pain associated with propofol injection, such as cooling propofol to 4 °C, injecting into a large vein, not using vessels on the back of hands, changing propofol formulation [3], using lidocaine mixed with propofol or before the injection, using dopamine antagonists (metoclopramide), using opiates [8], diluting propofol [9] and using the EMLA cream before injection [10-11]. Pretreatment with low doses of propofol, opiates and nonsteroidal anti-inflammatory drug, ketamine, esmolol/metoprolol, magnesium, use of light, combining clonidine/ephedrine, dexamethasone and metoclopramide have all been studied and have showed variable effectiveness [3].

Although many strategies have been described to reduce

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the injection pain of propofol, the most common method used in routine clinical practice is either adding 10-40 mg of lidocaine to propofol syringe immediately before injection, or pretreatment with lidocaine [12].

Propofol Lipuro 2% is a newly introduced formula of propofol [12], which is licensed for use in the UK and has recently been distributed in the Iranian market. Propofol Lipuro contains medium-chain triglycerides as lipid carriers [12-13]. It is suggested that dilution of propofol with medium-chain triglycerides reduces free propofol concentration in the aqueous phase to 39.9% and it also reduces the incidence of injection pain [14]. This is also proven in pediatric anesthesia [15].

Given that the propofol with 2% concentration has recently entered the Iranian market and the fact that it is more desirable than propofol 1% due to smaller consumption volume and being more economical, and because up to now there has not been sufficient studies on the amount or reduction of injection pain of propofol 2 %, this study was performed to evaluate the injection pain of propofol emulsion 1% (MCT/LCT), with emulsion of propofol 2% (propofolLipuro) in combination with 10 mg lidocaine anesthesia in gynecologic surgery on women.

Methods

This study is a double blind, randomized, controlled clinical trial carried out in 2015-2016 in Shahid Beheshti Hospital Center on 18-65 years old women with ASA1,2who were candidate for gynecologic surgery under general anesthesia. The study was approved by the Faculty Committee and the permission was obtained from the university ethics committee. Patients with previous allergic reaction to propofol, lidocaine, emulsion, fat and eggs or those with a history of soporific pillsor drugs, liver disease, renal failure, heart failure, neurologic or psychiatric symptoms, history of seizures, communication failure, hypovolemia, chronic pain, anxiety and lack of interest in cooperating were enrolled in the study.

Patients who needed a change in anesthetic drugs due to some side-effect incidence were also excluded from the study.

The sample size necessary for this study was calculated as 25 subjects in each group, with Confidence Interval of 95% and statistical power of 80% and also considering a significant difference of at least 0.8 between experimental groups. The patients were randomly allocated into 4 groups.

All patients avoided eating 8 hours before the operation. All of the patients were evaluated at the time of entering the operation room. A peripheral venous catheter (green cannula 22) was placed on forearm cubital vein. After admission to the operating room, all standard monitors such as pulse oximetry, ECG and blood pressure were connected to the patients; and all vital signs of the patients (systolic, diastolic and mean blood pressure, arterial blood oxygen saturation, and heart rate) were measured and recorded before beginning injection, immediately after injecting 25% of the drug (first injection) and 1 min after anesthetic induction (immediately after intubation) and 1 and 5 minutes after intubation. After anesthetic induction, if the patient experienced low blood pressure more than 30% of the baseline, she would receive 5 milligrams ephedrine; and if experienced bradycardia (HR≥50), she would receive 0.5 mg atropine. Any complication during the injection, including coughing, gagging, burning sensation, redness and hives in the vessel, were recorded in a questionnaire.

We placed two vessels in every patient and gave them 10cc loading ringer prior to induction. Biographic data of all patients including age, sex, weight, height, BMI and type of surgery were collected. Prior to the operation, the patients received no sedation as premedication.

Induction dose of anesthesia in all patients was 2 mg/kg of propofol solution.

The first group was induced with propofol emulsion of 1% (MCT/LCT, Fresenius cabi) in combination with 10 mg of lidocaine (1 cc lidocaine 1%) and the second group was injected with Propofol 1% with distilled water. The third group was injected with propofol 2% (propofolLipuro, B-BRAUN) with 10 mg lidocaine and the fourth group was injected with propofol 2% and 1cc distilled water.

The drugs were prepared by a anesthesia technician and the anesthesiologists injector was not aware of the type of drug injected. The injection pain was measured and recorded by patient's verbal and motion responses. The process was as follows:

After injecting 25% of the calculated dose, the severity of pain was assessed severity of pain was evaluated using McCrirrick and Hunter scale, based on the patient's verbal and motion reactions including facial expressions, pulling back the arms, or tearing (Table 1).

The severity of pain was recorded and then the rest of the drug (75%) was injected along with fast-acting narcotic fentanyl 2 µg/kg and intermediate-acting relaxants atrochromium 0.5 mg/kg. After 120 seconds, endotracheal intubation was performed by the anesthesiologist and the patient connected to the anesthesia machine.

Finally, the collected data were entered into the computer by using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The data were analyzed using chi square, t test and ANOVA with repeated observations.

Table 1- Assessment of Propofol injection pain according to the McCrirrick and Hunter scale [16].

Degree of pain	Response
None (0)	No response to questioning
Mild (1)	Pain reported in response to questioning alone without any behavioral signs
Moderate (2)	Pain reported in response to questioning and accompanied by behavioral signs, or pain reported without any questioning

Results

100 patients undergoing gynecologic and inclusion criteria were evaluated. All demographic factors such as age, height, weight and body mass index are presented in (Table 2). There was no significant difference among the four groups in any of these parameters.

Table 2- Frequency distribution of demographic characteristics for the patients in the study

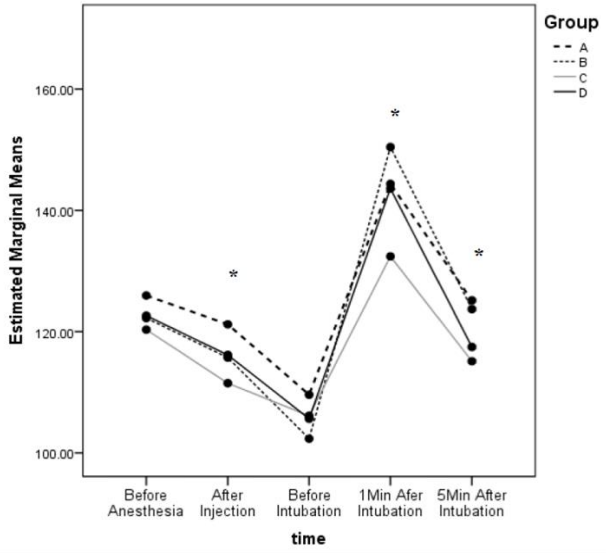
Groups Variable	Group A	Group B	Group C	Group D	p-value
Age (Year)	33.88 ±9.97	32.08 ±7.66	34.76 ±10.26	34.44±8.06	0.675
Height (Cm)	159.20 ±8.87	163.16 ±5.40	161.64 ±5.49	161.36±4.93	0.190
Weight (kg)	76.22 ± 12.16	79.96 ± 13.28	79.32 ± 15.95	81.60 ± 10.19	0.441
BMI (kg/m2)	30.26± 5.42	29.99± 4.51	30.22± 5.59	31.33± 3.64	0.150

Statistical significance: p<0.05

All vital signs were measured at intervals, before the induction of anesthesia, after injecting (25% of the drug), before intubation and at one and five minutes after intubation.

Significant differences were observed in the following intervals among groups: in systolic blood pressure (after injecting 25% of the drug, one and five minutes after intubation) and diastolic blood pressure (one minute one of intubation). Immediately after injecting 25% of the drug, the mean systolic blood pressure in group A was significantly higher than the mean in to group C. One minute after intubation, the mean systolic blood pressure in group C was significantly less than the other three groups of A, B, and D. Finally, five minutes after intubation, the mean systolic blood pressure in group A was significantly higher than groups C and D, and the mean systolic blood pressure of group C was significantly lower than group B (Figure 1). In the diastolic blood pressure, only in the first minute after intubation, the mean blood pressure of group Cwas significantly lower than group D. (Figure 2)

Figure 1- The linear graph of the changes in mean systolic blood pressure of the four groups of the study.

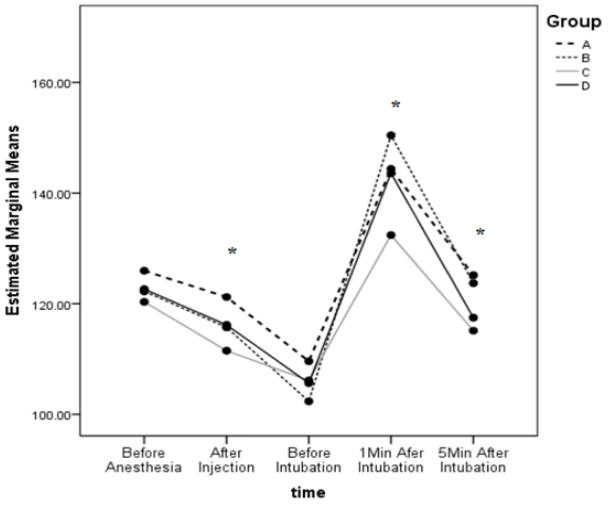


*marks significant differences among the four groups, p-value<0.05

A: propofol 1%+10mg Lidocaine, B: propofol 1%, C: propofol2%+10mg Lidocaine, D: propofol 2%

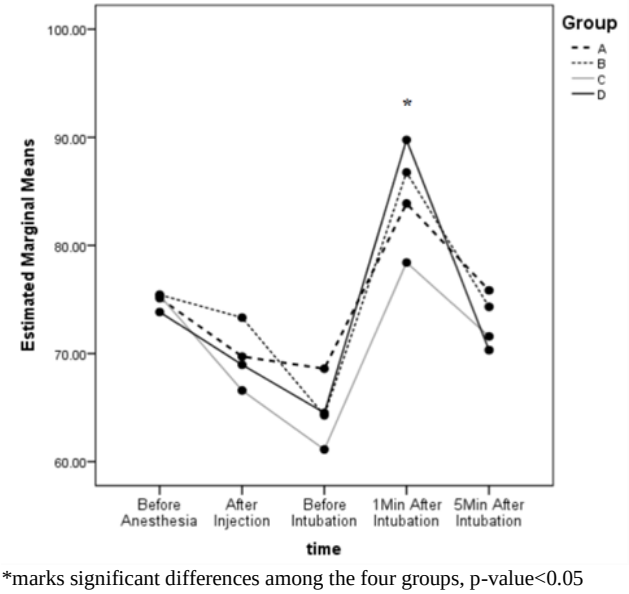
Regarding the mean arterial pressure, a significant difference was observed between the four groups only in the first minute after intubation, so that the mean arterial pressure in group C was significantly lower than group D and B (Figure 3).

Figure 2- The linear graph of the changes in mean diastolic blood pressure of the four groups of the study.



*marks significant differences among the four groups, p-value<0.05

Figure 3- The linear graph of the changes in mean blood pressure of the four groups of the study.

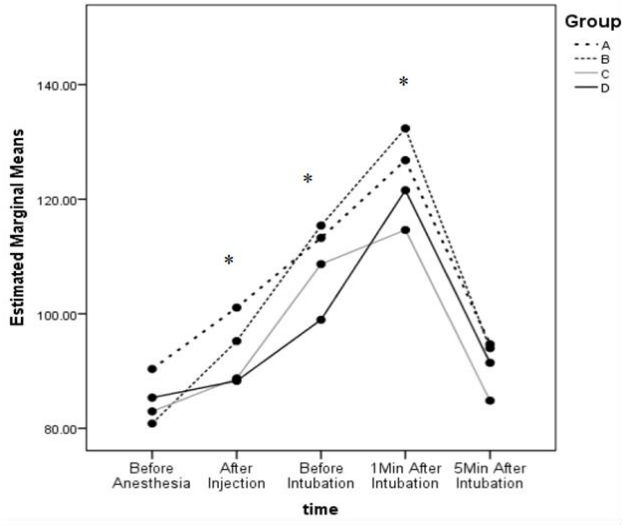


*marks significant differences among the four groups, p-value<0.05

The average heart rate, immediately after injecting 25% of the drug, before intubation and also in the first minute after intubation showed significant difference. Immediately after injecting 25% of the drug, the mean heart rate in group A was significantly higher than group D. Immediately before intubation, the mean heart rate of group D was significantly lower than groups A and B. And finally, one minute after intubation, the mean heart rate of group C was significantly lower than groups A and B and the mean heart rate of group D was significantly lower than group B (Figure 4).

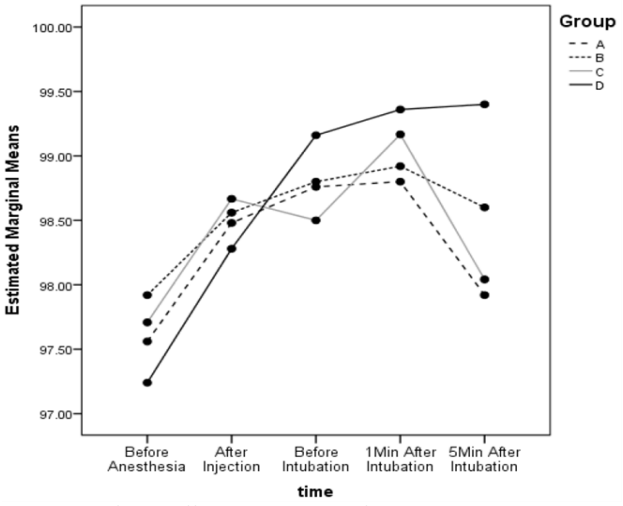
The results related to the determination and comparison of the mean blood oxygen saturation in various intervals of the study showed that the difference between groups was only significant in the minute five after intubation, so that the mean blood oxygen saturation in group A was significantly lower than group D. (Figure 5)

Figure 4- The linear graph of the changes in mean heart rate of the four groups of the study.



*marks significant differences among the four groups, p-value<0.05

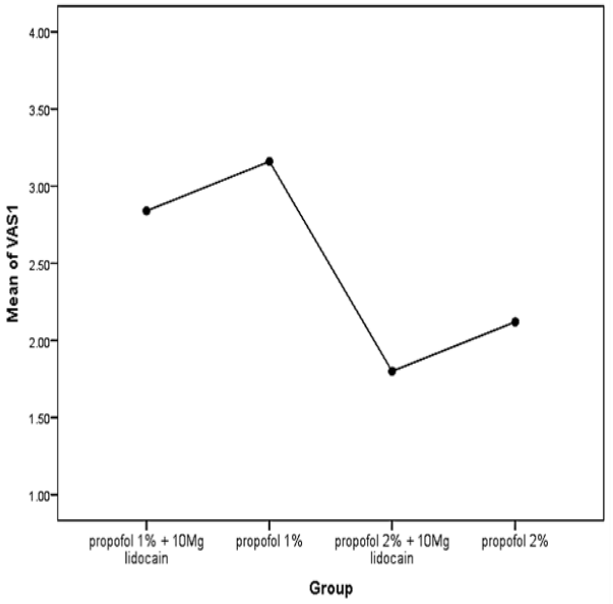
Figure 5- The linear graph of the changes in mean blood oxygen saturation of the four groups of the study.



*marks significant differences among the four groups, p-value<0.05

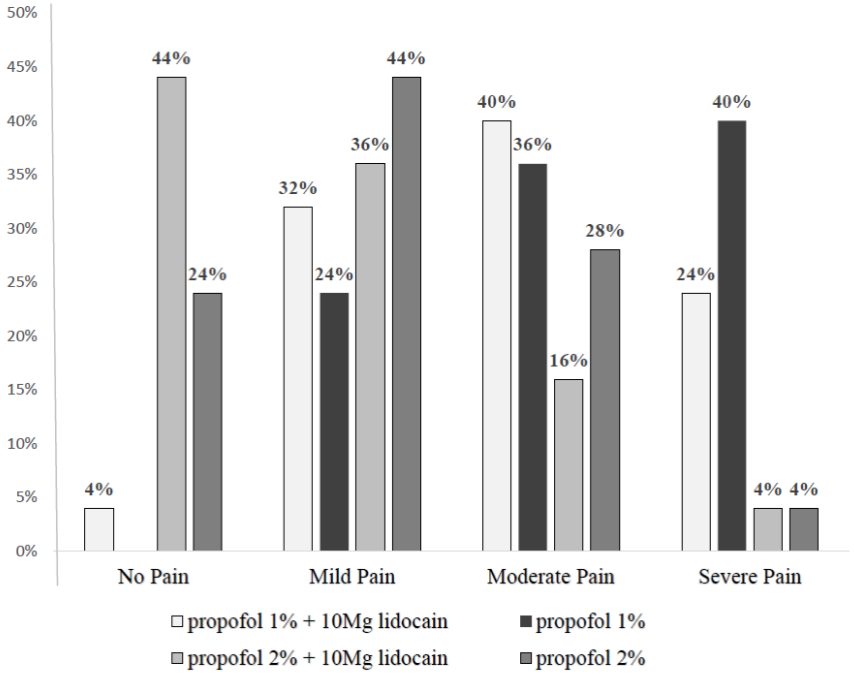
Regarding the mean of pain severity, there was a significant difference between the four groups of the study immediately after injection. The mean of pain severity in the two groups of A and B was significantly higher than the mean in groups C and D. However, there was no significant difference in the mean pain severity among groups A and B; in average, in the two groups who received propofol Lipuro 2% with 10 mg of lidocaine (group C) and the group receiving propofol 2% (group D) the pain severity was mild, while the pain severity was average in the group receiving propofol 1% with 10 mg of lidocaine (group A) as well as the group recipient of propofol 1% (group B) (Figure 6).

Figure 6- The linear graph of the changes in mean of pain severity among the four groups of the study.



A significant difference in the incidence of pain immediately after injection was observed among patients in the study groups. So that in the group receiving Propofol 1% with 10 mg lidocaine (Group A), The incidence of average pain was prevalent (40%). In the group receiving propofol 1% (Group B) the incidence of severe pain was prevalent (40%). In the group receiving propofol 2% with 10 mg lidocaine (Group C) the incidence of body pain was prevalent (44%) and in the group receiving propofol 2% (Group D) the incidence of mild pain was prevalent (44%). Also, it is noteworthy that out of 18 patients with severe pain, the highest number was in the group receiving propofol 1% (n = 10) and then in the group receiving propofol 1% with lidocaine 10 mg (n = 6). From total of 34 patients with mild pain, the highest number was in the group receiving propofol 2% (n = 11) and after that in the group receiving propofol 2% with 10 mg lidocaine (9 people). The prevalence of pain-free cases (11 out of 18 patients) was in the group receiving propofol 2% with 10 mg lidocaine and this number was significantly higher than other groups (Figure 7).

Figure 7- The prevalence of the pain severity in the four groups of the study.



Reading adverse side effects, no itching, coughing and gagging were observed in any patient in the groups. While the incidence of irritation in the vessels during injection (p-value = 0.001<0.05) and hives complication (p-value=0.001<0.05) were significantly different among the four groups, the frequency of red-vein complication (p-value=0.056>0.05) was not significantly different. Hives complication occurred only in 10% of patients (n=10) and its frequency in group B - recipient of Propofol 1% (n=8-80%) was significantly higher than the other three groups.

Bradycardia side effect did not occur in any of the four groups of the study at any time. Hypotension complication was observed only in 4 out of 100 patients (4%) in four groups, two cases (50%) in group B and 2 cases (50%) in group C. There was no significant difference in the incidence frequency of hypotension complication between the four groups.

The frequency of using atropine in four groups was zero. Two patients (50%) in Group B and 2 patients (50%) in Group C needed 5 mg of ephedrine. There was no significant difference in the ephedrine dose among the four groups.

Discussion

Propofol is used as an intravenous anesthetic drug which is favorable and excellent for a calm induction of anesthesia and has a speedy recovery. The drug belongs to the group of phenol.

Since the first clinical trial in 1977 [17], injection pain has been a major clinical problem.

It is expected that with the introduction of a new formulation, complications including injection pain use will not be a problem for usage of this drug.

So far, many studies have been carried out on how to reduce propofol injection pain [9-12,18].

In recent years, Propofol-Lipuro 2% (B Braun Ltd, Melsungen, Germany) was approved for use in the UK [18] and it has recently entered the Iranian market.

In this study, the patients who received a mixture of propofol 2% lipuro and lidocaine (10mg) experienced significantly less pain during anesthetic injection, compared to patients who did not receive lidocaine or induced with propofol1%. The incidence of injection pain in the control group that was recipient of propofol 1% was 76% and in the control group receiving propofol 2% was 32%, which clearly showed that propofol 2% Lipuro has less injection pain. This finding is consistent with the Doenicke's study [18].

In our study, 32% and 20% of the patients in the group receiving propofol 2% and the group receiving the combination of propofol 2% and lidocaine, respectively, experienced moderate and severe pain. But the incidence of moderate and severe pain in propofol 1% group and the combination of propofol 1% and lidocaine group was 76 and 64 percent, respectively; which partly confirms the study by Turan et al [19] who observed 23.34% pain reduction for propofol non-Lipuro in lidocaine group and also the study of Singh et al [20] who observed a 20% reduction.

The mechanism in which lidocaine makes injection of propofol painless is unknown. But it is said to be related to reduction of pH in propofol emulsion, which makes propofol in lipid phase and reduce its concentration in the aqueous phase; and this leads to pain reduction in propofol injection [21].

On the other hand, propofol can cause inflammation of the skin and mucosal and vascular intima. The mechanism of this inflammation, and the activity of Kinin–kallikrein system and finally the release of bradykinin that leads to vasodilatation and vascular permeability [20].

In our study, there was no significant difference among the four groups in the incidence of red veins. But the incidence of hives was observed in 10% of patients out of whom 80%

were in the control group recipients of propofol 1%. This shows that using the new formula of propofol with and without lidocaine has no role in hives complication.

Therefore, we can conclude that injecting propofol 2% in combination with 10 mg of lidocaine for anesthetic induction significantly reduces the average severity of pain and also significantly increases the frequency of painless state. After that, a significant reduction in the average pain severity and a significant increase in the frequency of painless state or mild pain in patients was observed in injection of propofol emulsion 2% alone in comparison to the injection of propofol emulsion 1% in combination with 10 mg lidocaine and injection of emulsion propofol 1% alone. Regarding the patient's vital signs, on average, systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate in injection of propofol 2% with 10 mg lidocaine was less than other three groups. While this reduction was only significant in some intervals of the study, there was no significant difference in the average blood oxygen saturation. The incidence of redness and irritation complications in the vein in patients who received propofol 2% in combination with 10 mg lidocaine was significantly lower than other patients. Therefore, considering the fact that this drug entered into the Iranian market and has less side effects, can be used for induction of anesthesia adding 10 mg lidocaine.

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