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The Effect of Propofol Infusion Before Administration of Its Bolus Dose on Propofol Injection Pain and Serum Complement C3 Levels; A Randomized Clinical Trial

Behrooz Zaman [1], Samad Noorizad [1], Seydalireza Seyed Siamdoust [1], Mahzad Alimian [1,*] and Sara Parak [2]

[1] Pain Research Center, Iran University of Medical Sciences, Tehran, Iran
[2] Department of Anesthesia, Iran University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Pain Research Center, Iran University of Medical Sciences, Tehran, Iran. Tel: +98-9123070413, Email: alimian.m@iums.ac.ir

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Abstract

Background: Pain on injection with propofol is still a major problem associated with anesthesia. Several factors involved in this event have been studied with respect to their pain attenuating effects.
Objectives: The purpose of this study was to evaluate the effect of propofol infusion before administration of its bolus dose of propofol on the resulted pain at its induction dose and on serum complement C3 levels.
Methods: This clinical trial was performed on patients undergoing surgery under general anesthesia divided into three groups, including A (without intervention), B (propofol infusion at a dose of 50 μg/kg/min before anesthesia induction), and C (propofol infusion at a dose of 100 μg/kg/min 100 before anesthesia induction). During anesthesia induction by propofol, the presence, absence or severity of pain was determined using the Numerical Rating Pain Scale. Serum complement C3 levels were measured and their relationships with pain scores were compared between three groups. The data were analyzed using SPSS V. 22 software.
Results: There were significant differences in the mean pain scores between three groups ($P < 0.05$). However, no significant difference in the mean pain scores was observed between the groups B and C ($P > 0.05$). The mean and standard deviation of the differences in complement C3 values in the three groups before and after injection were 72.15 ± 14.9, 27.65 ± 9.82, and 18.95 ± 4.68, respectively, which demonstrated a significant difference between three groups ($P < 0.05$). However, the difference in complement C3 values between the groups B and C was not significant ($P > 0.05$).
Conclusions: According to the obtained results, the low doses of infused propofol, 2 minutes before administration of its bolus dose, seems to have a considerable attenuating effect on its pain score.

Keywords: Complement C3, Infusion, Propofol Injection Pain

1. Background

Propofol is a phenol derivative and intravenous anesthetic agent with short duration of action. It is characterized by a rapid onset of action and recovery time, which made it be used as drug of choice in almost all surgical procedures. Due to its rapid onset and short duration of action, easy titration, and fewer side effects, it has been administered as a selective agent for general anesthesia in millions of patients each year (1). In spite of its positive features, 60% of patients have reported pain during propofol injection and in 20% of them a severe and intolerable pain has been announced (2). Most of patients have found it the as the most painful phase of their preoperative procedures (3). Regarding the mechanism of this pain, it should be noted that when the active component of aqueous phase of propofol comes into contact with vascular endothelium and intravascular nerve endings, it activates the inflammatory kallikrein - kinin system, which, in turn, activates bradykinin and complement C3 (4). Although there was no difference in the amount of the inflammatory factors between LCT and MCT propofol, the bradykinin production and the complement C3 activation are recognized as the inflammatory markers for propofol injection pain (5).

Various studies have been conducted to reduce this pain using different agents, including lidocaine, fentanyl, ketamine, dexmedetomidine, etc. The impact of Gabapentin, which impedes the release of nociceptive neurotransmitters, such as noradrenaline, substance P, and

glutamate, and consequently prevents the onset of pain, has been investigated in recent studies (5-7). Kang et al. investigated the effect of age, sex, and injection site on the pain, induced by propofol injection (8). In another study, Ohmizo et al. compared long-chain triglyceride (LCT) emulsive propofol with long-medium chain triglyceride (LCT/MCT) emulsive propofol in terms of their impact on injection pain (4).

One of the practical methods to reduce the pain associated with painful stimulants is the gradual administration of low-dose stimulant, which lessens the sensitivity to the stimulant effects and increases the threshold of pain perception; this mechanism is called low-dose desensitization (9). The limited numbers of clinical experiments as well as the results of some clinical trials have shown that the onset of propofol infusion 2 minutes prior to the administration of its bolus dose, can diminish its injection pain, which might be due to the reduced vascular wall sensitivity (or desensitization) to the propofol-induced inflammatory stimulation and its associated pain (10).

In a clinical trial in 2011, Shimizu et al. studied 120 patients as the candidates for elective orthopedic surgery. The patients were assigned randomly and equally into four groups, and the effects of fast and slow injection of propofol were compared with lidocaine. The results showed that the injection-induced pain was lower in the group with rapid injection of propofol (11).

In another clinical trial by Kodaka et al., 200 patients undergoing elective surgeries were included in the study. They allocated the participants into 4 groups: group I (LCT control), group II (LCT/MCT control), group III (LCT study), and group IV (LCT/MCT study). Groups III and IV received propofol infusion (0.1 mg/kg) before induction. Based on their results, 36 patients (72%) in the LCT control group and 31 patients (62%) in the LCT/MCT control group experienced pain and also 21 subjects (42%) in the LCT study group and 24 subjects (48%) in the LCT/MCT study group experienced pain. Their results indicated that propofol infusion (0.1 mg/kg) prior to its bolus dose relieved propofol-induced injection pain (12).

By activating the Kinin - kallikrein system and releasing bradykinin, propofol causes vasodilatation, vascular permeability, and increased contact of the aqueous phase propofol with free nerve endings, resulting in pain on injection, as well as inflammation of the skin and mucosal and vascular intima (13-15).

The complement C3 is synthesized in the liver and macrophages and is the main element of the complement system. It should be activated to develop the complement cascade. This factor is rapidly generated and activated in a few seconds in both classical and alternative pathways in all parts of the body that are infected or inflamed. It is divided into two components, namely C3a and C3b. C3b plays an important role in localized inflammatory reactions and has a half-life of 5 to 30 minutes. The complement system activity can generate several chemotactic peptides by the absorbance of neutrophils and eosinophils. In infections, C3a and C5a, both activate mast cells and stimulate platelets to release histamine and serotonin. They increase the vascular permeability and cause secretion of lysosomes from neutrophils and Thromboxane from macrophages, and may cause tissue damage in severe cases.

Several methods have been used to attenuate the pain on injection with propofol. Adding lidocaine to propofol, cooling or warming propofol, diluting propofol solution, injecting propofol into a large vein, pre-treatment with IV injection of lidocaine, ondansetron, metoclopramide, and an opiate, or thiopental with or without a tourniquet have led to different results in attenuating pain on injection with propofol (3, 15-17). Propofol emulsions contain medium- and long-chain triglycerides (MCT and LCT). Various studies have been reported that 1% MCT/LCT propofol reduces the incidence and severity of injection pain compared to the LCT propofol (18-20).

Accordingly, in this research, we decided to conduct a more comprehensive study, investigating the effect of propofol infusion at two different doses (50 and 100 μg/kg/min) 2 minutes before administration of its bolus dose, and also evaluating the complement C3 levels.

2. Methods

This study was a single-blinded, randomized clinical trial. The study population included patients as the candidates for surgery under general anesthesia in the affiliated hospitals of Iran University of Medical Sciences in 2017 - 2018. After obtaining the approval from the institutional ethics committee (Approval code: IR.IUMS.REC.1395.9311174005) and also the informed consent from the patients, they were randomly assigned into 3 groups (A, B, and C). Using 40% difference between the groups (α = 0.05 and β = 0.2), approximately 20 samples were considered in each group to prevent no decrease in samples using the test power of 90% and the significant P value of less than 0.05%. The study was also registered at the ClinicalTrials.gov (IRCT20170301032837N2). The inclusion criteria included the patients candidate for general anesthesia aged 18 - 60 years, the American Society of Anesthesiologists (ASA) physical status I and II, no history of reaction to propofol and the consent of patients. Exclusion criteria also included the patients who were candidates for general anesthesia younger than 18 or older than 60 years,

ASA physical status > II, a history of reaction to propofol and the patient's withdrawal from the study.

After an intravenous cannula fixation on the dorsum of the patients' hand, 5 mL of blood was taken from all patients in each group to measure complement C3a (for baseline sample). In all three groups, anesthesia was induced by midazolam (2 mg), fentanyl (3 μg/kg), propofol (2 mg/kg) and atracurium (0.5 mg/kg). The injection speed of propofol was the same in three groups. In group A, we just used the induction dose of propofol, and 2 minutes after IV cannula placement and blood sampling, anesthesia was induced. In group B, the infusion of propofol at 50 μg/kg/min was performed and 2 minutes later, the bolus dose was administered. In group C, propofol infusion at a dose of 100 μg/kg/min was administered 2 minutes before induction. In all three groups, one minute after administration of bolus propofol, 5 mL of blood was sampled from ipsilateral antecubital vein and sent to the laboratory to measure activated complement C3 using immunoturbidimetric method.

Only a researcher who evaluated the pain and filled out the questionnaire was blinded to the patients' group assignment. The presence or absence of pain during induction was assessed by the Numerical Rating Pain Scale (NPRS) with four different scales: grade I: no pain (0); grade II: mild (grimacing) (1, 2, 3); grade III: moderate (expression of pain and grimacing) (4, 5, 6); and grade IV: severe pain (withdrawal of hand) (7, 8, 9, 10). It is designed for patients aged over 9 years. NPRS is verbally scored from 0 to 10. The zero score represents the absence of pain, whereas 10 score indicates the worst pain ever possible (21)

Using a questionnaire, the patients' information, including their medical records, blood tests and laboratory tests results, and also their reported pain scores was collected and analyzed by SPSS V. 22 software. In analyzing descriptive data, quantitative variables were expressed as mean and standard deviations, and the qualitative variables were expressed as the percentage and frequency. For quantitative variables, the normal distribution of data was first examined by the one-sample Kolmogorov-Smirnov test and, accordingly, the analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare these variables in three groups. Chi-square test or Fisher's exact test was used to compare qualitative variables in groups. The significance level was set at 0.05.

3. Results

Descriptive and comparative characteristics of the serum complement C3 levels in patients undergoing surgery under general anesthesia in three groups, without propofol infusion, propofol infusion with a dose of 50 μg/kg/min, and propofol infusion with a dose of 100 μg/kg/min are illustrated in Table 1. The results did not show a significant difference in serum complement C3 levels in groups before injection ($P > 0.05$). However, there were significant differences in serum complement C3 levels in patients receiving the bolus doses of propofol in all groups ($P < 0.05$). There was also a significant difference in the fluctuation of serum complement C3 levels in patients undergoing surgery under general anesthesia before and after injection in all three groups ($P < 0.05$).

Table 2 shows the descriptive and comparative characteristics of pain scores in three groups, including the group without propofol infusion, propofol infusion at a dose of 50 μg/kg/min group, and the group with propofol infusion at a dose of 100 μg/kg/min. The pain intensity was associated with the bolus injection of propofol in all three groups ($P < 0.05$).

4. Discussion

The obtained results indicated that propofol infusion at a dose of 50 or 100 μg/kg/min prior to a bolus injection of propofol in groups B and C, compared to the control group, was effective on the attenuation of injection-induced pain. However, no significant difference was observed between propofol infusions at the doses of 50 or 100 μg/kg/min.

Evaluation of the serum complement C3 levels in all three groups before and after bolus injections of propofol demonstrated that propofol infusion before its bolus dose in both B and C groups led to obvious differences in the serum complement C3 levels.

However, limited studies have been conducted to compare the effect of high and low doses of propofol infusion on pain reduction following propofol injection. Liljeroth et al. found that the onset of moderate or severe pain caused by intravenous propofol injection can be reduced by a low-dose propofol infusion within 2 minutes before induction, as a readily applicable technique, which is consistent with our results (22). In another study, Soltesz et al. observed no significant difference between propofol 0.5% and propofol 1% (standard formulation) in the severity of pain on propofol injection in children aged 2 - 6 years (23). Grauers et al. also found no significant differences in the intensity and duration of pain induced by propofol injection (1 mL/s within 2 seconds and 0.2 mL/s within 10 seconds) in patients undergoing plastic or ear, nose and throat (ENT) surgery, which is consistent with our results (24).

In another study, Kodaka et al. reported that a low dose of propofol (0.1 mg/kg) administered prior to anesthesia induction, reduced the injection pain (12). The results of this study are in line with our findings.

Table 1. Descriptive Characteristics and Comparison of the Serum Levels of Complement C3 (mg/dL) in Patients Undergoing Surgery Under General Anesthesia in Three Groups, Without Propofol Infusion and with Propofol Infusion at the Doses of 50 and 100 μg/kg/min

Measurement Time (mg/dL)	Group[a]			Intergroup Comparisons	
	A	B	C	Test Statistic	P Value
Before injection	100 ± 5.86	106.45 ± 12.58	108.2 ± 13.34	2.23	0.11
After injection	172.15 ± 7.3	134.1 ± 16.35	127.15 ± 27.31	5.18	0.009
Mean differences before and after the injection	72.15 ± 14.9	27.65 ± 9.82	18.95 ± 4.68	5.24	0.008
In-group comparisons					
Test statistic	3.83	4.59	3.92		
P value	0.001	< 0.001	< 0.001		

[a]Values are expressed as mean ± SD.

Table 2. Descriptive Characteristics and Comparison of Pain Scores in Patients Undergoing Surgery Under General Anesthesia in Three Groups, Without Propofol Infusion and with Propofol Infusion at the Doses of 50 and 100 μg/kg/min

Pain Intensity	Group[a]			Intergroup Comparisons	
	A	B	C	Test Statistic	P Value
Without pain	0 (0)	16 (80)	12 (60)	49.59	< 0.001
Mild	1 (5)	4 (20)	6 (30)		
Moderate	6 (30)	0 (0)	1 (5)		
Severe	13 (65)	0 (0)	1 (5)		

[a]Values are expressed as No. (%).

Soltani Mohammadi et al. demonstrated that decreasing the proportional volume of propofol as an induction agent for patients undergoing elective surgery resulted in pain reduction following intravenous injection (25). In another study, Pellegrini et al. found that there was no difference in the intensity of pain on intravenous injection in children undergoing ENT surgery between the propofol 1% and propofol 2% groups. Therefore, they concluded that for anesthesia induction in children undergoing ENT surgery, different propofol concentrations was associated with similar pain reduction during injection (13), which is no consistent with the results of study. Hirmandpour et al. observed that in patients undergoing gynecologic surgery under general anesthesia, the propofol injection pain was greater in the propofol 1% group than that of the propofol 2% group, which can be due to the patients' genetic, ethnic, and cultural differences in pain perception between both groups (14).

The results of the present study indicated that the administration of propofol prior to the injection of its induction dose, at both doses of 50 and 100 μg/kg/min, had a significant effect on the reduction of serum complement C3 level in patients undergoing surgery under general anesthesia in both groups B and C compared to the group A. However, propofol infusion at 100 μg/kg/min had the same effect compared to the propofol infusion at 50 μg/kg/min on the complement C3 reduction. Accordingly, propofol infusion before anesthesia induction at an effective dose of 50 μg/kg/min seems to be an appropriate choice to alleviate pain during propofol injection and reduce complement C3 level.

4.1. Conclusions

Low doses of propofol infusion administered prior to its bolus dose seem to trigger desensitization in the vascular endothelium and decrease the inflammatory reaction induced by the bolus injection of propofol, resulting in reducing the stimulation of nerve endings located in the inner layer of the vascular wall and attenuating the pain perceived by patients.

Although the pain scores in the intervention groups were lesser than that of the control group, further and more precise studies are required to prove this finding.

Future studies using different doses of propofol and techniques are recommended to be designed.

Footnotes

Clinical Trial Registration Code: The study was registered at the ClinicalTrials.gov (Ref: IRCT20170301032837N2).

Conflict of Interests: The authors declare that there are no conflicts of interest in this study.

Ethical Approval: The study was approved by the institutional ethics committee of Iran University of Medical Sciences (Approval code: IR.IUMS.REC.1395.9311174005)

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Patient Consent: The informed consent was also obtained.

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