Journal of Advances in Medicine and Medical Research

Volume 36, Issue 10, Page 208-214, 2024; Article no.JAMMR.123895
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Effect of Different Propofol Preparations on Injection Pain

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Authors' contributions

This work was carried out in collaboration between both authors. Authors OY and DC designed the study, performed the statistical analysis, wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i105604

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/123895

Original Research Article

Received: 21/07/2024
Accepted: 24/09/2024
Published: 26/09/2024

ABSTRACT

Aim: Propofol is an intravenous anesthetic agent that is frequently used. However, it has a disadvantage that it causes pain during injection. This pain can be quite uncomfortable for patients. Propofol preparations containing oil emulsion at various concentrations have been produced to relieve pain. We aimed to compare the effects of preparations with different propofol concentration, lipid content and lipid chain structure Propofol 1% and Propofol 2% on injection pain and hemodynamic response.
Study Design: Prospective, randomized and single-blind study.
Place and Duration of Study: Department of Anesthesiology and Reanimation, University Hospital, between July 2019- December 2019.
Methodology: Patients aged 18-65 years, who underwent general anesthesia for elective hysteroscopy were included. In our study, one group (Group P1) was given propofol 1% and the

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Cite as: *Yılmaz, Ozlem, and Dilek Cetinkaya. 2024. "Effect of Different Propofol Preparations on Injection Pain". Journal of Advances in Medicine and Medical Research 36 (10):208-14. https://doi.org/10.9734/jammr/2024/v36i105604.*

other group (Group P2) was given propofol 2%. The patient's pain was evaluated and recorded at the 5th, 10th and 15th seconds according to the Verbal Rating Scale (VRS).
Results: One hundred patients were evaluated. The mean pain scores of the patients were 0.24 (0-2) at the 5th second, 0.96 (0-3) at the 10th second and, 1.22 (0-3) at the 15th second in Group P1, 0.92 (0-3) at the 5th second, 1.76 (0-3) at the 10th second and, 2.00 (0-3) at the 15th second in Group P2. These values were statistically significant (P< 0.05).
Conclusions: We concluded that the approach of increasing the lipid content by increasing the propofol concentration applied in this study is not sufficient to reduce the incidence of pain, and that the fatty acid chain length, as well as the propofol concentration, are among the important factors affecting the formation of pain.

Keywords: Propofol; propofol injection pain; propofol emulsions; pain with propofol.

1. INTRODUCTION

Propofol is an intravenous anesthetic agent that is frequently used in general anesthesia induction, day surgery, intubation and invasive procedures in intensive care units. The rapid onset of its effect, rapid recovery, easy titration, and reduction of postoperative nausea and vomiting are the reasons why it is frequently preferred [1]. However, it has a disadvantage that it causes pain during injection and this pain occurs more frequently if a vein on the dorsum of the hand is used. While the incidence of pain is 28-85% in children, it ranges from 28-90% in adults [2]. This pain can be quite uncomfortable for patients. Some patients remember the induction of anesthesia as the most painful part of the perioperative period. Many factors such as the location of the injection and the diameter of the vessel used, the injection speed, the buffering effect of the blood and, the temperature of the propofol affect the frequency of pain [3,4]. Numerous drugs such as lidocaine, opioids, magnesium, thiopental, ondansetron, metoclopramide, ketamine, and topical nitroglycerin have been used to prevent injection pain caused by propofol [5-8].

Propofol preparations containing oil emulsion at various concentrations have been produced to relieve pain. The aim is to reduce the free concentration of propofol in the aqueous phase by being absorbed by the fat particles [9,10]. The length of the fat chains added to propofol is also one of the factors affecting pain. Studies have reported that while more pain is seen with preparations containing only long-chain fatty acids (LCT), less injection pain is seen with propofol preparations containing both medium (MCT) and long-chain fatty acids [11].

In our study, we aimed to compare the effects of preparations with different propofol concentration, lipid content and lipid chain structure Propofol 1% (10 mg/ml propofol and 50 mg/ml MCT) and Propofol 2% (20 mg/ml propofol and 100 mg/ml MCT and LCT on injection pain and hemodynamic response.

2. MATERIALS AND METHODS

Our study was initiated after receiving approval from our hospital ethics committee (11.04.2019/17) and our country medicines and medical devices agency (27.05.2019/66175679-511.14-E.85748). Patients aged 18-65 years, ASA I-II, who underwent general anesthesia for elective hysteroscopy between 01.06.2019 and 01.01.2020 were included in the study. Patients with ASA III-IV-V, who have received or are undergoing psychiatric treatment, who use chronic analgesics, who have taken analgesics (Nonsteroidal anti-inflammatory drugs) in the last 24 hours, who are addicted to alcohol/drugs, who take steroid therapy, who have liver and kidney failure, who are allergic to propofol, and cancer patients was excluded.

During the preoperative preanesthetic visit, informed consent forms were obtained from the patients stating that they voluntarily participated in the study. In our prospective, randomized and single-blind study, randomization was performed using the closed-envelope method. The patients were divided into two equal groups as Group P1 (propofol Lipuro 1%, B.Braun®) and Group P2 (propofol 2% Fresenius®). The drugs were prepared in 20 cc syringes and administered by the anesthesiologist-physician who was unaware of which drug was used. Drug administration and pain assessment were performed by the same anesthesiologist-physician. Demographic data of the patients such as age, height and weight were recorded.

Standard monitoring was performed on patients who were taken to the operating room without premedication. A vascular access was opened

with a 20-gauge venous cannula on the non-dominant back of the hands of the patients and saline infusion was started. The propofol preparation, which was previously determined by the sealed envelope method, was administered at a dose of 2-3 mg/kg by keeping it at room temperature for 30 minutes before injection. During induction, propofol was administered at a constant rate of 1 ml over 2 seconds. The patient's pain was evaluated and recorded at the 5th, 10th and 15th seconds according to the Verbal Rating Scale (VRS). When the patient had very severe pain, the injection was stopped and patients were excluded from the study by administering lidocaine. Side effects such as local redness, urticaria, and edema that occurred during the application were also noted. Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) and Oxygen saturation (SpO2) measurements were recorded before and after propofol injection. The study was terminated when the patient was unconscious. Then, standard anesthesia induction was continued and 0.5 mg/kg lidocaine and 0.5-1 mcg/kg remifentanil were administered, and the surgical procedure was started by placing a laryngeal mask for airway maintenance.

2.1 Statistical Analysis

In the statistical analysis of the data, continuous data are given as mean ± standard deviation. Categorical data are given as a percentage (%). Shapiro Wilks test was used to investigate the suitability of the data for normal distribution. Two-way repeated measures ANOVA (Single Factor Repeated) test was used for repeated measurements. Pearson Chi-Square and Pearson Exact Chi-Square analyzes were used in the analysis of the created cross tables. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the analysis. A sample of 60 people was used with 80% power to detect an effect size of 0.4277 using a 3-degree-of-freedom Chi-Square Test with a significance level of 0.05.

3. RESULTS

A total of 104 patients were included in the study. But in 2 patients, the injection was stopped due to severe pain and they were excluded from the study. Two patients were also excluded because they wanted to withdraw from the study. One hundred patients were evaluated.

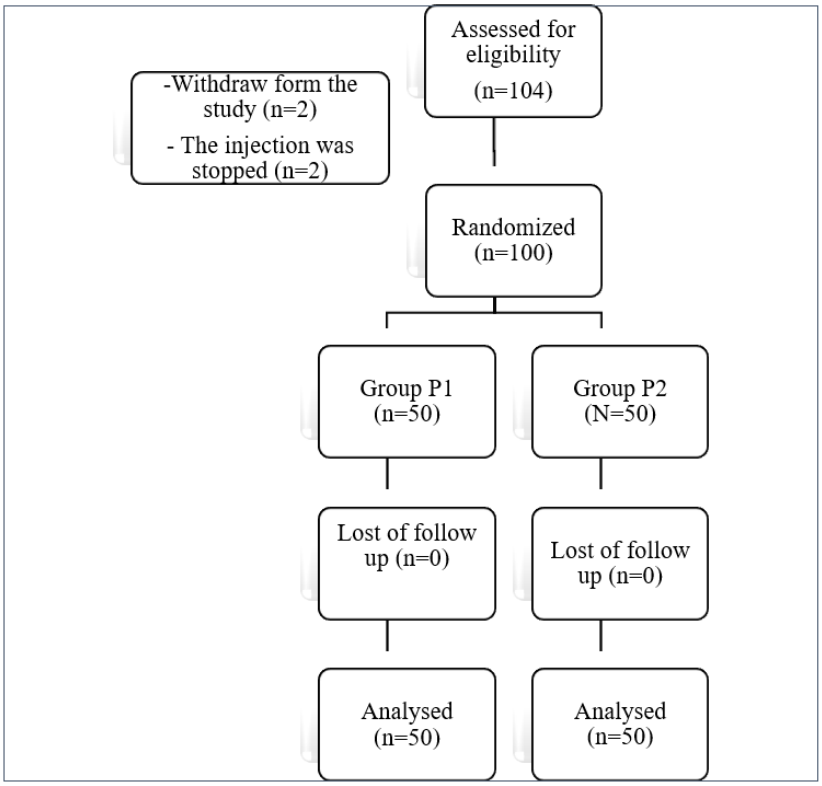

Fig. 1. CONSORT

Table 1. Demographic characteristics of patients

	Group P1 (n=50)	Group P2 (n=50)	P value
Age	39.5 ± 9.64	37.7 ± 9,82	0.35
Weight (kg)	70.9 ± 13.52	68.4 ± 15.13	0.40
BMI (kg/m2)	27.1 ± 4.98	25.6 ± 5.74	0.19
HT	6 (12%)	5 (10%)	0.85
Asthma	3 (6%)	3 (6%)	1.00
Hypothyroidism	3 (6%)	7 (14%)	0.63
DM	4 (8%)	4 (8%)	1.00
COPD	0	1 (2%)	1.00

HT: hypertension, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease Data are presented as mean ± standard deviation and per cent.

Table 2. Pain scores of patients

Pain score	Group P1 Mean(min-max)	Group P2 Mean(min-max)	P value
5 second	0.24 (0-2) §	0.92 (0-3) §	0.003*
10 second	0.96 (0-3) §	1.76 (0-3) §	<0.001*
15 second	1.22 (0-3) §	2.00 (0-3) §	<0.001*

*In-group comparison *P<0.05, between-group comparison §P< 0.05*

Table 3. Maximal pain score (VRS)

Pain score	Group P1 (n=50)	Group P2 (n=50)
0 = no pain	13 (26%)	4 (8%)
1 = mild pain	14 (28%)	11 (22%)
2 = moderate pain	22 (44%)	16 (32%)
3 = severe pain	1 (2%)	19 (38%)

Data are presented as %.

The mean of patients age was 39.5 ± 9.64 years in Group P1 and 37.7 ± 9.82 years in Group P2. While the body weights of the patients were 70.9 ± 13.52 kg in Group P1, 68.4 ± 15.13 kg in Group P2, their body mass indexes (BMI) were 27.1 ± 4.98 kg/m2 in Group P1, 25.6 ± 5.74 kg/m2 Group P2. The most common co-morbid disease in the patients was found to be hypertension with 11%. There was no statistically significant difference between the groups in terms of demographic characteristics (Table 1).

The mean doses of propofol administered to the groups was found to be 182.6 ± 19.78 mg in Group P1, and 180.0 ± 20.20 mg in Group P2. There was no statistically significant difference between the doses of propofol administered (P= 0.517).

The mean pain scores of the patients were 0.24 (0-2) at the 5th second, 0.96 (0-3) at the 10th second, 1.22 (0-3) at the 15th second in Group P1 and, 0.92 (0-3) at the 5th second, 1.76 (0-3) at the 10th second, and 2.00 (0-3) at the 15th second in Group P2. It was observed that the pain score increased in relation to the duration, and this increase was statistically significant. When we compared the pain scores between the groups, it was seen that the pain scores in Group P2 were higher than Group P1 in all three measurements, and these values were statistically significant (P<0.05). (Table 2).

In the comparison between the groups, the number of patients with no pain (VRS=0) in Group P1 was 13 (26%), while it was 4 (8%) in Group P2. There was one patients (2%) with severe pain (VRS=3) in Group P1, and 19 (38%) in Group P2 (Table 3).

When we look at the changes in the hemodynamic data, the post-induction heart rate of the patients decreased in both groups compared to the entry values, but this decrease was not statistically significant in intragroup comparisons. When we compared between the groups, it was seen that after induction HR decreased statistically significant more in Group P1 than in Group P2. Systolic, diastolic and mean arterial blood pressure values were found to be decreased compared to base values in post-induction measurements. However, this decrease was not statistically significant within and between-group comparisons.

No local side effects were encountered during propofol administration.

4. DISCUSSION

Propofol, like all phenols, is irritating to the skin and mucous walls. Propofol-related injection pain is caused by irritation of the vascular endothelium with a direct irritant effect in the early period, and due to the release of bradykinin from the kinin cascade in the late period. Another mechanism advocated in the formation of pain is that propofol causes neuropeptide release, peripheral nerve activation, neurogenic inflammation, and central sensitization in the spinal dorsal horn via TRPA1 and TRPV1 molecules [12,13]. In propofol emulsion, the drug is distributed differently in two phases: the outer aqueous phase and the inner lipid phase. With bolus injection, the external aqueous phase comes into contact with the venous endothelium, causing pain [14].

In the study conducted by Wang et al. [15] on 448 patients, 91.5% of the patients did not remember any discomfort and pain during the anesthetic injection in the postoperative period; and of those who remembered propofol-related injection pain, 89.5% felt mild pain, 7.9% felt moderate pain, and 2.6% felt severe pain. In our study, the incidence of pain was 74% in the group using propofol 1% (28% mild pain, 44% moderate pain, 2% severe pain), and 92% in the group using propofol 2% (22% mild pain, 32% moderate pain, 38% severe pain).

Klement et al. [9] suggested that propofol-related injection pain was related to the propofol concentration in the aqueous phase and not caused by the formulation. They diluted propofol with intralipid and 5% glucose solution and found that the pain was lower in the group diluted with 10% intralipid compared to the group diluted with 5% glucose. They concluded that pain increased with increasing propofol concentration, and decreased injection pain by reducing the concentration of propofol in the aqueous phase with intralipid. Another study compared injection pain in patients given propofol-MCT/LCT, propofol-LCT and 20 mg lidocaine before propofol-LCT. The researchers reported that the least pain was experienced in the lidocaine group and the most pain was experienced in the propofol-LCT group [16]. In this study, unlike our study, the propofol concentration in the preparations was the same but agents with different lipid contents were used.

Song et al in which low-lipid propofol (Ampofol®: 1% propofol, 5% soybean oil and 0.6% egg lecithin) and high-lipid propofol (Diprivan®: 1%

propofol, 10% soybean oil and 1.2% contains egg lecithin) were compared, there was no difference between the two preparations in terms of anesthesia onset time, induction rate, and anesthetic dose requirements; the incidence of pain was 39% in the low-lipid propofol group and 9% in the high-lipid group (P<0.05). Ampofol with a low lipid content was associated with a more frequent incidence of pain during injection [17].

We used Propofol-Lipuro® (propofol emulsion containing 10 mg/ml propofol, 50 mg/ml MCT, propofol 1%) and Propofol 2% Fresenius® (20 mg/ml propofol, 100 mg/ml MCT/LCT, propofol 2%) in our study. Contrary to what was advocated, we observed that the approach of increasing the lipid content as the propofol concentration applied during the preparation of Propofol 2% did not reduce the incidence of pain. We found that the pain scores of the propofol 2% group with higher lipid content were statistically significantly higher than the propofol 1% group. We attributed this to the higher concentration of propofol in propofol 2% and the presence of long chain in the content of propofol 2%, and the co-existence of medium chain fatty acids in 1% of propofol. When we examined the relationship between the pain scores of the patients and the duration, it was observed that the pain scores of both groups increased significantly in relation to the duration, and the highest pain score was measured at the 15th second. We opine that this could be attributed to the propofol-related delayed injection pain.

As a result; we concluded that the approach of increasing the lipid content by increasing the propofol concentration applied in this study is not sufficient to reduce the incidence of pain, contrary to what is advocated, and that the fatty acid chain length, as well as the propofol concentration, are among the important factors affecting the formation of pain. We believe that preparations containing medium chain fatty acids are more effective in reducing injection pain.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards and/or our university standards, patient(s) written consent has been collected and preserved by the author (s).

ETHICAL APPROVAL

The study was approved by Eskişehir Osmangazi University Clinical Research Ethics Committee (11.04.2019/17) and Turkish Medicines and Medical Devices Agency of the Ministry of Health of the Republic of Turkey (27.05.2019/66175679-511.14-E.85748).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/123895