



# Effects of Pre-treatment with Ketamine and Tourniquet Application on the Prevention of the Pain Induced by Propofol Injection: A Randomized Controlled Clinical Trial

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## ABSTRACT

**Introduction:** The pain induced by propofol injection is a common adverse complications caused by propofol, which is ranked seventh among the 33 clinical symptoms of anesthesia. The present study aimed to investigate the effects of pre-treatment with ketamine and tourniquet inflation on the pain induced by propofol injection.

**Methods:** This randomized controlled clinical trial was conducted on 120 patients with the American Society of Anesthesiologists (ASA) physical status classification I. The patients were assigned to six groups. In groups one and four, tourniquet was inflated above the angiocatheter. In groups two and five, ketamine was injected 30 seconds before propofol injection with no tourniquet. The patients in groups three and six were injected with propofol alone. To assess the severity of pain, verbal rating scores were used. Data analysis was performed in SPSS version 20.

**Results:** In total, 74 male and 46 female patients were examined. In terms of pain severity, the lowest level of pain was experienced with the injection of ketamine before propofol with the use of a tourniquet (groups one and four). Based on the injection site, the total pain scores were higher with the injection of propofol into the veins on the dorsum of the hand. In addition, the mean pain score in groups one, two, four, and five was significantly lower compared to groups three and six ( $P < 0.05$ )

**Conclusion:** According to the results, use of ketamine, especially with a tourniquet, could alleviate the pain induced by propofol injection.

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## Introduction

Propofol is the most common sedative-hypnotic drug used for the induction and maintenance of anesthesia in operating rooms and intensive care units owing to its rapid onset of effects, short-term duration of action, and ease of titration (1,2). Despite the mentioned advantages, propofol causes major side-effects, such as reduced blood pressure, respiratory depression, and pain upon injection (3).

tion (3).

The pain induced by propofol injection is a common complication of this drug, which is ranked seventh among 33 clinical symptoms of anesthesia (4-6). The prevalence of pain upon the injection of propofol has been estimated at 68-90% (7). Most patients have described this pain to be severe.

Various interventions have been performed to

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prevent the pain induced by propofol. Such examples are narcotic injection (8), heating and cooling, drug dilution, injection through larger veins, prescription of various premedications, and intravenous on-site lidocaine injection. However, there are still no urgent strategies for the prevention of this pain (9).

Pre-injection of ketamine has been reported to be an effective strategy to prevent the pain induced by propofol injection (9-11). Ketamine is a general anesthetic that could induce anaesthesia via the inhibition of N-methyl-d-aspartic acid (NMDA) receptor complex and providing significant analgesia (10,11). Furthermore, ketamine could prevent the reduction of blood pressure caused by propofol-induced anaesthesia (11).

Despite the beneficial effects of ketamine, it has some unintended effects, such as hallucination, increased systemic blood pressure and heart rate, and increased intracranial and intraocular pressure, which have led to the restricted use of this agent (12).

To date, few studies have been focused on the effectiveness of ketamine in the alleviation of the pain induced by propofol injection (9). The present study aimed to investigate the effects of pre-treatment with ketamine on the pain induced by propofol injection.

## Methods

This double-blind, randomized clinical trial was conducted on 120 patients aged more than 12 years with the American Society of Anesthesiologists (ASA) physical status classification I. The patients were candidates for general anesthesia with propofol.

The study protocol was approved by the Institutional Review Board and Ethics Committee of the university, and written informed consent was obtained from all the patients; in case of the patients aged less than 18 years, consent was obtained from their legal guardian.

The exclusion criteria of the study were as follows: 1) history of drug abuse; 2) alcohol consumption; 3) consumption of analgesic drugs within 24 hours before the operation; 4) history of epilepsy and cardiovascular, renal, and liver diseases; 5) pregnancy; 6) neurological disorders; 7) Glasgow comma scale scores of <15 and 8) presence of contraindication for propofol injection.

Demographic data of the patients were recorded, including age, body weight, and gender. The insertion site of the angiocatheter was determined by a ward nurse who was blinded to the study based on the routine guidelines. If the angiocatheter was on the forearm of the patients, they were randomly assigned to groups one, three or five. If

the angiocatheter was on the dorsum of the hand, the patients were randomly allocated to groups two, four or six.

The patients were routinely monitored in terms of pulse oximetry, noninvasive blood pressure, electrocardiogram, and capnography during anaesthesia, and recovery (with the exception of ETCO<sub>2</sub>). Patients in groups one and four had a tourniquet above the injection site, which was inflated equal to the measured systolic blood pressure, and ketamine was injected (0.1 mg/kg; CU Chemie Uetikon, GmbH, Germany). After 30 seconds, the tourniquet was deflated, and propofol (Diprivan, AstraZeneca, USA) was injected at the dosage of 2-2.5 mg/kg. In groups two and five, ketamine was injected (0.1 mg/kg), and after 30 seconds, propofol was administered (2-2.5 mg/kg). In groups three and six, only propofol was injected (2-2.5 mg/kg).

Data were collected using the questionnaires of pain severity, which were completed by a nurse who was blinded to the research. To do so, a curtain was installed between the anaesthesiologist who injected the drugs and the nurse who recorded pain severity. During the injection of propofol in all the study groups, the nurse measured the pain severity based on the verbal rating score.

Pain measurement was performed based on the verbal rating score on a four-point scale. The patients were instructed on reporting their pain severity; score zero was used to express no pain, and scores one, two, or three were used to express pain after the injection of propofol. Score one described mild pain, score two described moderate pain, and score three described severe pain. The obtained results in this regard were recorded by the nurse.

If the vein path was inflamed (red, swollen, painful, and hot) or dislodged, a nurse who had no role in the research procedures established an intravenous line from the forearm or back of the patient's hand in accordance with the hospital guidelines.

Data analysis was performed in SPSS version 20, and the data were described using central tendency indices (mean, mode, and standard deviation). In addition, the Kruskal-Wallis test was used to assess the correlations between the variables, and student t-test, analysis of variance (ANOVA), and paired t-test were applied to compare the data before and after the intervention. Chi-square test was also used for the analysis of the quantitative variables. In all the statistical analyses, P-value of less than 0.05 was considered significant.

## Results

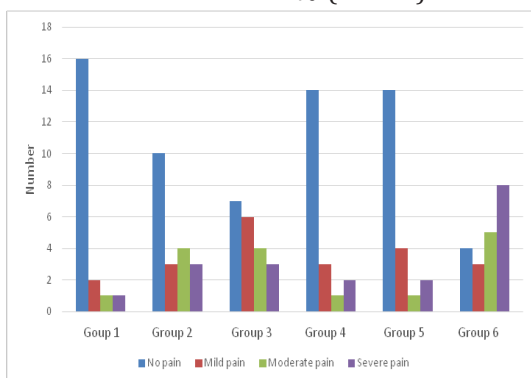
In total, 120 patients were enrolled in the present study. The demographic characteristics of

the patients are presented in Table 1. According to the findings, there were significant differences

**Table 1.** Demographic Characteristics of Study Groups.

Groups	Sex		P-Value	Age			P-Value (Total)
	Male	Female		Male	Female	Total	
1	11	9	0.87	35.18± 13.65	34.88± 13.29	33.05± 14.01	0.92
2	11	9		35.9± 13.69	33± 14.31	34.6± 13.96	
3	9	11		32.9± 12.27	33.8± 15.66	32.9± 13.89	
4	13	7		35.45± 15.46	34.1± 16.88	34.85± 6.38	
5	11	9		38± 11.52	38.2± 14.03	38.1± 12.46	
6	10	10		32.18± 16.054	38.2± 11.56	34.9± 13.99	

As is depicted in Diagram 1, the injection of ketamine before the administration of propofol on the forearm of the patients with a tourniquet (group one) caused pain in 20% of the patients ( $P=0.05$ ). In group two, four, and five, the sensation of pain was reported by 50%, 30%, and 30% of the patients, respectively. In group three, in which the patients were only administered with propofol via injection into the forearm, 65% of the patients reported the sensation of pain. In group six, the highest rate of pain reported by the patients with propofol injection into the back of the hand was estimated at 80% ( $P=0.04$ ).



**Diagram 1.** Pain severity score in study groups.

## Discussion

According to the results of the present study, ketamine injection along with the application of tourniquet before propofol injection could effectively reduce the severity of the pain induced by propofol injection. To date, several methods have been proposed for the alleviation of the pain induced by propofol injection; such examples are the use of isoflurane gas, injection of magnesium sulfate, cooling of the drug to the temperature of 4°C, and use of thiopental (8,9). These methods have yielded variable results regarding the reduction of the pain induced by propofol injection. The current research also aimed to investigate the reduction of pain severity by the injection of ket-

amine before propofol injection and assess the effect of tourniquet placed above the injection vein.

between the study groups in terms of the complaint of the pain induced by propofol injection ( $P=0.005$ ).

In the present study, the patients were selected based on the ASA-PS 1 in order to prevent the possible effect of the clinical status due to systemic diseases on the severity of pain in the patients. Ketamine is considered to be an NMDA receptor antagonist. According to Wolf and Winkson, increased peripheral and central sensitivity is the consequence of NMDA receptor activation in the posterior horn of the spinal cord (17). Furthermore, ketamine could exert similar effects to narcotics through occupying the muscarinic and glutamate receptors, which in turn results in analgesic effects. According to the findings of the current research, severe pain was experienced by only two patients in the study groups receiving ketamine injection along with a tourniquet (1.66%). Seemingly, ketamine could accumulate in the veins below the tourniquet and induce local anesthetic effects. Furthermore, our findings indicated that in the groups receiving ketamine injection without tourniquet inflation before the injection of propofol, 20% of the patients reported no pain as opposed to 9.16% of the patients in the groups administered with no ketamine. The results obtained by Woo Koo Seung are consistent with the current research in terms of the analgesic and anesthetic effects of ketamine (9).

According to the study by Borazan et al. (15), using a tourniquet before ketamine injection could effectively diminish the pain induced by injection without the need for the use of narcotic drugs and methods, which may adversely affect the central nervous system. This finding is in line with the results of the present study.

In addition to investigating the effectiveness of ketamine injection along with a tourniquet, we evaluated the effect of angiocatheter insertion site. Accordingly, severe pain due to propofol injection into the forearm was experienced by five patients as opposed to 13 patients with injection

into the back of the hand, which might be due to the differences in the anatomic and physiological characteristics of the veins in these areas.

One of the limitations of the present study was the difference in the gender of the patients between the study groups. However, we attempted to control this limitation by increasing the sample size in each group. Therefore, it is recommended that similar studies be conducted after eliminating the limitation of the gender factor by investigating equal numbers of male and female patients since this factor could affect the severity of the pain reported by patients.

## Conclusion

According to the results, the pain induced by propofol injection could decrease significantly through the prior injection of ketamine (0.1/kg of body weight), along with the placement of a tourniquet above the injection vein. In case no tourniquet is used, the selection of a vein on the forearm could reduce the incidence of pain compared to injection into the back of the hand.

## Acknowledgements

None.

## Conflict of Interest

The authors declare no conflict of interest.

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