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Research Article

The Effect of Premedication with Oral Acetaminophen on the Prevention of Localized Pain Resulting from Intravenous Propofol Injection: A Randomized Double Blind Placebo Clinical Trial

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ABSTRACT

Background: Propofol is one of the most widely used medications in anesthesia and intensive care. Propofol Intravenous injection is painful for patients at the injection site. The aim of this study was to determine the effect of premedication with oral acetaminophen in prevention of local pain caused by intravenous injection of propofol.

Methods: This study was a double-blind randomized controlled trial. Data were collected from July 2020 to July 2021 in Shariati Hospital. All stages of premedication and induction of anesthesia were the same in all three groups of patients. Pb, P500 and P1000 groups (patients with oral placebo, 500 or 1000 mg of oral paracetamol, respectively) received the medication 1 hour before transfer to the operating room.

Results: In this study, 150 patients were included. 44.7% were men, 55.3% women, and mean age of patients was 36.82 ± 10.24. The highest severity of reported pain was in the group of patients receiving placebo. Patients receiving 1 gram of acetaminophen had the lowest reported pain. Patients receiving 500 mg of acetaminophen reported significantly less pain than patients receiving placebo and more pain than patients in the group receiving 1 g of acetaminophen. Age, gender and weight did not have any significant effect on the pain severity.

Conclusion: When compared to placebo, the use of oral acetaminophen as a premedication considerably lowers discomfort induced by intravenous propofol infusion. A dosage of 1 g of oral acetaminophen is more effective than 500 mg in decreasing pain. The level of pain and acetaminophen's pain-relieving effects were not affected by age, gender or weight.

Introduction

Acetaminophen is one of the most popular and widely used painkillers in the world. Its exact mechanism of action is complex and not fully known but seems to cover both central and peripheral analgesic pathways. It is a para-aminophenol derivative, and an analgesic antipyretic medication that causes its analgesic effect by inhibiting central prostaglandin synthesis with minimal inhibition of peripheral prostaglandin synthesis, with very little and rare side effects in analgesic doses in otherwise healthy patients. [1-3] of course, some have mentioned that it does not have any peripheral effect. Acetaminophen is almost entirely

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This drug has rare side effects in analgesic doses in otherwise healthy patients. It does not cause platelet disfunction [4] or gastric mucosal problems [2]. It is metabolized in the liver, and the minor metabolites are responsible for the hepatotoxicity seen in overdose [5]. Inducers of the cytochrome P450 enzyme system in the liver (such as alcohol) increase the formation of metabolites and therefore increase hepatotoxicity. In certain patients (chronic ethanol users, malnutrition, and fasting patients), repeating therapeutic or slightly excessive doses may precipitate hepatotoxicity.

The oral form of paracetamol appears to have different pharmacokinetic and pharmacodynamic forms than intravenous form [6]. Acetaminophen is completely and rapidly absorbed following oral administration, with bioavailability around 85% to 95% after first-pass metabolism. Peak serum concentrations are achieved within 2 hours and therapeutic serum concentrations are 10 to 20 μg/mL [7]. About 90% of acetaminophen is hepatically metabolized to sulfate and glucuronide conjugates for renal excretion with a small amount secreted unchanged in the urine [8].

Propofol, a hypnotic alkylphenol derivative, is one of the most widely used medications in anesthesia and intensive care. This dose-dependent drug has various effects on physiological systems. Propofol does not have analgesic effects. Intravenous injection of propofol is painful for patients at the injection site. This can be especially annoying for patients with thinner, more fragile arteries, children, and patients with skin and vascular diseases. Therefore, the aim of this study was to determine the effect of premedication with oral acetaminophen on the prevention of local pain caused by intravenous injection of propofol.

It is commonly believed that preoperative administration of acetaminophen reduces the pain of propofol injection with a dose-dependent pattern. Canbay et al [9] showed that the pain rate of propofol injection was 64% in the control group and 22% in the intravenous form of acetaminophen group. The results of the study by Khouadja et al. [10] were similar: the reported pain was 85% in the control group and 36.6% in the intravenous paracetamol group.

Methods

This study was a double-blind randomized controlled trial (RCT). For this study, the permission of the medical school and the ethics committee of Tehran University of Medical Sciences were obtained (IR.TUMS.MEDICINE.REC.1399.383). Also, it was approved by national board of randomized clinical trial (IRCT20210511051268N1).

Patient selection and data collection

Data were collected from July 2020 to July 2021 in Shariati Hospital. A total of 150 patients with the American Society of Anesthesiology (ASA) class I to III who were between 18 and 65 years old, and all within the normal BMI range (less than 25 and more than 18) were included in the study scheduled for non-emergency surgeries who all had a 20 gauge intravenous catheter on the dorsum of their hand.

Exclusion criteria included weight less than 50 kg, chronic pain in any part of the body, hypertension, cardiovascular disease or cerebrovascular disease, difficulty communicating (even if there is a marked decrease in level of consciousness with the initial injection dose), cirrhosis or abnormal liver function test (AST and ALT more than twice normal) Kidney failure or creatinine clearance more than 1.2 and sensitivity to either acetaminophen or propofol. Also, those who did not have a venous catheter on the back of their hands, or those whose catheter size was not 20 gauge, or those who had to use rapid sequencing for anesthesia induction, were excluded from study.

Randomization and blinding

Randomization was performed using the block-of-6 chain method. Both the patient and an independent evaluator (in charge anesthesia) were unaware of the type of oral medication. Also, the person in charge of statistical analysis was unaware of the grouping of patients and patients were enrolled the initial analysis by coding.

Intervention

All stages of premedication and anesthesia induction were the same in all three groups of patients. Pb, P500 and P1000 groups (patients with oral placebo, 500 or 1000 mg of oral paracetamol, respectively) received the drug 2 hour before transfer to the operating room. Each patient received 2 placebo tablets (Pb group), 1 placebo tablet and 1 (500 mg) paracetamol tablet (P500 group) or 2 (500 mg) paracetamol tablets (P1000 group). Placebo and acetaminophen were the same in shape, size, color and weight. The costs of acetaminophen and placebo were voluntarily provided by the person in charge of the research (anesthesiology resident) and no cost was imposed on the patients. Propofol was used for induction of anesthesia, like other patients not enrolled in the study. Propofol was administered with perfuser pumps with the aim of delivering detailed and precise doses.

None of the patients received any injectable analgesics or other sedatives. Of course, patients referred to shariati hospital operation room, on the recommendation of preoperative anesthesia consult (unless contraindicated or interfering with the patient's own medication), receive chlordiazepoxide tablets the night before surgery and 2 hours before surgery, with a little bit water, to relieve preoperative anxiety.

Before anesthesia induction, patients were pre-oxygenated with 100% oxygen for 2 minutes with simple face mask. At the time of drug infusion, all patients had a simple oxygen mask with a flow rate of 4 lit/min. Patients were monitored with BIS (Bi-spectral index Score) to

measure the level of consciousness, with a goal of BIS more than 80 after administration of the initial dose of propofol to keep awake and communicably. All patients were provided by 20% of the total amount of propofol induction doe (2 mg/kg) in order to evaluate the severity of pain resulting from injection on the dorsum of hand. Any patient with BIS below 80 after injection of the initial dose was excluded from the study. Awake patients were asked to score their pain severity using the standard 11-point verbal numerical rating (VNRS). a 1% emulsion of propofol was used and dosage was calculated according to lean body mass (LBM). The propofol used in this study was an emulsion under the brand name Propofol-Lipuro 10mg/ml, made in Germany (B BRAUN company). The crystalloid solution prescribed for intravascular fluid management (normal saline 500 ml per hour).

The perfuser syringe extension tube was connected to the patient by a simple Cath-TEC model three-way in the middle of the normal saline injection route. During the initial dose of the drug, the serum route was closed and the desired amount of drug was injected directly from the perfuser to the patient, without dilution with serum. After delivery of a quarter of the calculated dose of propofol, the perfuser was temporarily stopped, saline was given to deliver the administered dose, and the patient was asked to rate his or her pain. After completing the questionnaire and scoring the pain, or for those excluded from the study due to BIS below 80, continuation of the induction dose was injected along with other necessary drugs for general anesthesia.

Statistical Analysis

Statistical analysis was performed using SPSS software version 26 (SPSS, Chicago, IL, USA). The mean and standard deviation (SD) of continuous variables were calculated. Categorical variables were presented as the number of patients and percentage. Continuous variables were analyzed using ANOVA or the Kruskal-Wallis test. Also, Fisher or Chi-square tests were used to analyze data. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, 150 patients were included. Of these, 44.7% were men (n=67) and 55.3% (n=83) were women. The mean age of patients was 36.82 ± 10.24. The mean weight was 74.31 ± 6.85 and the mean pain intensity was 4.98 ± 3.37. The results of statistical analysis of statistical relationships are shown in (Table 1).

According to the results, pain intensity in patients was significantly different based on the dose received (p <0.001). The highest severity of reported pain was in the group of patients receiving placebo. Patients receiving 1 gram of acetaminophen had the lowest reported pain. Patients receiving 500 mg of acetaminophen reported significantly less pain than patients receiving placebo and more pain than patients in group 1 g of acetaminophen (Figure 1).

Due to the fact that pain intensity can be considered as a qualitative ranking variable, chi-square test was used to investigate the relationship between pain intensity (ranking quality) and gender variable (female/male) (Table 2). The test results showed that there was no significant relationship between gender and pain intensity ($\chi2=14.73$, $p = 0.12$). Kendall's Tau-b correlation test was used to evaluate the correlation (Table 3) between pain intensity and age, weight and dose of the medication.

According to the results of the drug dose-correlation test, it was inversely and strongly correlated with pain intensity ($p <0.001$). No statistically significant correlation was found between reported pain intensity, age and weight of patients ($p> 0.05$).

Multiple linear regression analysis (Table 4) was used to predict pain intensity. The results of statistical modeling showed that, in general, the model is statistically significant ($\beta = 9.03$, $p <0.001$). Gender did not differ significantly in predicting the reported pain intensity. However, the dose of the drug could significantly predict the severity of pain ($\beta = -3.94$, $p <0.001$). In fact, if acetaminophen (500 mg) is replaced with placebo, the pain intensity will be reduced by 3.94 units. Also, if the dose of the drug is increased from 500 mg to 1 g of acetaminophen, the intensity of pain reported by patients will be reduced by 3.94 units.

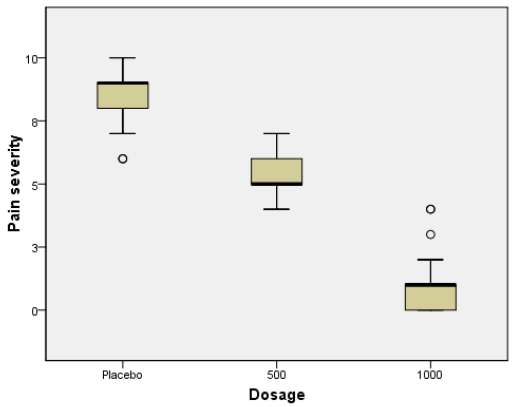

Figure 1- Comparison of pain intensity in 3 groups of patients receiving placebo, 500 & 1 g acetaminophen.

Table 1- Comparison of pain intensity based on demographic characteristics of patients

Variable	Mean ± SD	Test statistics	P value
Pain severity (according to dosage)		F= 862.77	P<0.001
Placebo	8.67±1.04		
500 mg	5.30±0.86		

1000 mg	1.00±0.94		
Pain severity (according to gender)		t = 0.27	0.74
Male	4.90±3.16		
Female	5.05±3.54		
Pain severity (according to gender)		t = -0.10	0.91
=< 70 kg	4.96±3.47		
> 70 kg	5.02±3.17		
Pain severity (according to gender)		t = 1.78	0.07
=< 35 years old	5.54±3.39		
> 35 years old	4.47±3.29		

Table 2- Comparison of pain intensity based on the received dose of oral acetaminophen

	Dosage		
	500	**1000**	**P value**
	Mean ± SD	**Mean ± SD**	
Pain severity	5.3±0.84	1.0±0.94	<0.001

Table 3- Correlation of pain intensity with three variables of age, weight and drug dose

	τb	**P value**
Pain & dosage	-0.86	<0.001
Pain & age	-0.12	0.086
Pain & weight	0.016	0.816

Table 4- Linear regression model to predict patients' pain intensity

	β	**95% CI**	**P value**
Dosage	-3.94	- 4.13 to - 3.75	<0.001
Gender	-0.25	-0.57 to 0.056	0.10
Overall model	9.03	8.75 to 9.32	<0.001

Discussion

Propofol, a hypnotic alkylphenol derivative, is a short-acting intravenous anesthetic that reduces the level of consciousness and is one of the most widely used drugs in anesthesia and intensive care [11]. It is used to induce anesthesia as well as to maintain anesthesia during surgery and, to a lesser extent, to provide sedation in the operating room or intensive care unit for adults who are under mechanical ventilation. Propofol also has anticonvulsant and anti-nausea effects and has a very fast recovery. The maximum effective time of this drug is about two minutes and in some cases between five to ten minutes. This drug has side effects from intravenous injection. Some of the side effects of this drug are decreased heart rate (bradycardia), hypotension, pain and burning sensation at the injection site and apnea [11]. It is recommended that it be used in combination with narcotic drugs such as morphine, as it has no analgesic effects [12].

The study of Afhami et al. [13] with the aim of determining the effect of ephedrine in reducing pain caused by injection of Propofol in the induction phase of anesthesia, showed that in terms of pain intensity in the control group, 30 patients had moderate pain, 19 patients had mild pain and only one patient was painless. These amount in the case group were 0, 10 and 40, respectively (p <0.001). The effect of sex on pain was not significantly. They conclude that Ephedrine premedication not only alleviates or relieves pain at the propofol injection site, but also significantly reduces hypotension following propofol injection.

The results of a similar study [14] show that hydrocortisone and lidocaine reduced pain during propofol injection. Therefore, the use of these drugs may reduce the pain of propofol injection. The dose of lidocaine 2% was 1 mg/kg, and hydrocortisone dose was 25 mg. This difference, however, was not significant between the lidocaine and hydrocortisone groups. The impact of hydrocortisone and lidocaine on pain severity was likewise not significant when gender, age, and weight were considered.

Shoeybi et al [15] showed that injection of 8 mg dexamethasone before propofol injection significantly reduces the severity and incidence of pain during propofol injection.

In a study by Safavi et al [16], the results showed that 80% of patients in the control group (placebo or normal saline) compared to 34% in the magnesium sulfate group, 38% in the ketamine group and 18% in lidocaine group had pain during propofol injection (P <0.01). Compared with saline group, the incidence of mild, moderate and severe pain in the group of "ketamine", "lidocaine" and "magnesium sulfate" was significantly reduced (P <0.05). Intravenous injection of magnesium sulfate, lidocaine

and ketamine has almost the same effect on reducing pain during propofol injection and there is no preference between them. Of course, all three drugs were intravenous medications. The main difference between the present study and the mentioned studies was the oral route of acetaminophen administration as a premedication, two hours before anesthesia induction.

A similar study in 2018 [17] shows that oral paracetamol in the form of premedication can reduce the dose-dependent pain in intravenous injection of propofol. They used 500 mg or 1 gram acetaminophen. However, they prescribed acetaminophen 1 hour before surgery, we have administered acetaminophen 2 hours before surgery. The findings of this study are completely in line with the results of our research and confirm the accuracy of our findings. In contrast 324 patients were enrolled. Pain intensity was lower in both 500 mg and 1000 mg groups (mean VNRS 2 and 4, respectively) than in the placebo group ($P < 0.001$). Interestingly, Pain was lower in the 1000 mg (70.4%) group than in the 500 mg and placebo groups (86.1 and 99.1%, respectively; $P < 0.001$). The present study also emphasizes that a dose of 1 g of oral acetaminophen is more effective than a dose of 500 mg as well as a placebo (respectively). Use of BIS for evaluating level of consciousness, and administration of a precise dose of drug using a perfuser pump, were among the differences of our study with theirs.

Khodja et al. [18] showed 85% in the control group 36.6% pain on propofol injection site in the group respectively. The incidence of pain during propofol injection was 85%, 36%, 21%, in the placebo group, intravenous paracetamol and lidocaine, respectively. According to the previous study, we decided to compare the analgesic effect of oral acetaminophen in three different doses.

The aim of this study was to determine the effect of pre-medication with oral acetaminophen on the prevention of localized pain from intravenous propofol injection. Our findings showed that the use of oral acetaminophen as a premedication to reduce the pain of intravenous propofol injection compared to placebo is significantly more efficient and useful. In fact, it significantly reduced patients' pain. Comparison between two doses of oral acetaminophen shows that a dose of 1 gram can reduce pain more effectively and significantly. No significant relationship was found between pain intensity and gender, age and weight of patients. In fact, the drug is able to reduce patients' pain in both sexes, age and weight and according to previous existing data from studies, using acetaminophen has promisingly decreased post operative pain [19] and reducing use of opioids in the pre-operative periods and therefore, eliminating the incidence of post operative nausea and vomiting (PONV) and GI paresis. However, it is reported that there is no difference between oral vs intravenous in terms of opioid use and PONV [20].

Limitations

It is suggested that this study be performed on a larger sample size using different drugs. Also, due to decreased level of consciousness with higher doses of propofol, serial evaluation of patients' pain intensity was not possible. Vital signs and hemodynamic parameters should also be considered in assessing pain quality. Finally, this was a single-center study and it is better to performed future studies in multi-center settings.

Conclusion

The use of oral acetaminophen as a premedication significantly reduces pain caused by intravenous propofol injection, compared to placebo. A dose of 1 g of oral acetaminophen has a better effect on reducing patients' pain than 500 mg. The severity of pain and the response to the pain-reducing effects of acetaminophen do not depend on age, sex, or weight.

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