

Ondansetron Pretreatment Reduces Pain on Injection of Propofol

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Abstract- To assess the effectiveness of ondansetron pretreatment in alleviating propofol injection pain, 135 patients were randomly assigned to one of following three groups. Group 1 who received up to 2 mL pretreatment 50 mg tramadol in the saline, group 2 cases who received up to 2 mL pretreatment 4 mg ondansetron in saline, and group 3 who received up to 2 mL solution saline. A 20 gauge cannula was placed into the largest vein on the dorsum of the hand. Tourniquet was closed to the arm above the cannula and inflates to 70 mmHg, and then drug was injected. After 20 seconds, the tourniquet deflated, and propofol 2mg/kg injected over 10 seconds and pain assessment was made. Results: Tramadol and ondansetron significantly reduced the incidence and severity of propofol injection pain more than placebo ($P=0.001$). The efficacy of ondansetron in alleviating the pain on injection of propofol was no different from tramadol ($P=0.330$). Ondansetron pretreatment may be used to reduce the incidence of pain on injection of propofol, an advantage added to the useful prevention of postoperative nausea and vomiting.

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Introduction

Propofol is considered as the induction agent of choice for day-care ophthalmic procedures. Propofol is a common intravenous (IV) anesthetic drug, used for induction and maintenance during general anesthesia with rapid onset and short duration. However, the incidence of pain following propofol injection is seen in almost 70% of patients, in the absence of other pretreatments (1-3). The quality of pain was described as extremely sharp, aching or burning. It has been arranged as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists (4). The mechanism by which propofol induces pain on injection has remarked unclear, although, numbers of different interventions have been used to alleviate pain produced by intravenous injection of propofol (1). Tramadol is a centrally acting weak μ -receptor agonist and inhibits nor-adrenaline re-uptake likewise promotes serotonin release (5). Wong and Cheong reported that pretreatment with tramadol was as effective as lidocaine in alleviating pain on propofol injection (6).

Ye *et al.*, demonstrated that ondansetron, a specific 5-HT antagonist, blocks Na channels in rat brain neurons. They also found that ondansetron is 15 times

more potent than lidocaine in causing numbness when injected under the skin (7).

Ondansetron has been showed to be an effective alternative (8,9).

Recently, some studies demonstrated that ondansetron is a well-established agent for prevention of postoperative nausea and vomiting after eye surgical procedures (10-13), and is used at our center. However, till date, there is relatively very little published data on the efficacy of ondansetron on the pain on injection of propofol. Thus, we postulated that intravenous ondansetron pretreatment might also reduce pain on injection of propofol. This study evaluated the effectiveness of ondansetron and tramadol pretreatment for alleviation of pain on propofol injection.

Materials and Methods

The study was approved by the Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran. The study was conducted at the Farabi Eye Hospital Complex, affiliated to Tehran University of Medical Sciences, Tehran, Iran. Written informed consent was obtained from all patients. One hundred thirty five patients (16-80) years old, American Society of Anesthesiologists physical status I and II, undergoing

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Effect of ondansetron pretreatment on the propofol injection pain

elective eye surgeries (Deep vitrectomy-lensectomy-full thickness corneal laceration-buckle) using general anesthesia, were included in this randomized prospective double-blinded and placebo- controlled study.

Patients with known hypersensitivity to propofol(Claris –chacharwadi-basana-ahmedabad,ondansetron (Tehran shimi-iran)or tramadol,(Tehran shimi -iran) concomitant analgesic or sedative medication; presence of infection on the dorsum of the left hand; indications for rapid sequence intubation; presence of cardiac conduction defects; epilepsy; and use of antiarrhythmic medications, thin dorsal veins, and uncooperative patients were excluded.

In our study, patients randomly assigned to three groups of 45 patients. No premedication was administered. A 20-gauge cannula was placed into the largest vein on the dorsum of the left hand after placing the routine monitors include lead II electrocardiogram, noninvasive blood pressure and pulse oximeter.

Patients received up to 2 mL pretreatment 50 mg tramadol in the saline (group 1),

4 mg ondansetron in the saline (group 2), solution saline (group 3) intravenously for a period of 10 seconds while the venous drainage was occluded by placing an air-filled tourniquet (pressure inflated to 70 mm Hg) on the upper arm by an assistant (14).

A blinded anesthetist prepared the solutions, and the investigator did not know the contents of the solutions. The occlusion was released after 20 seconds. Then 2 mg/kg propofol 1% was injected for a period of over 10 seconds. The drugs in the study were preservative free and at room temperature. No analgesic or sedative was administered before propofol. Another clinician, unaware of the group to which the patients had been allocated, assessed the level of pain on injection of

propofol. The patients were asked a standard question, “Is the injection comfortable?” The verbal response and behavioral signs, such as facial grimacing, arms withdrawal, or tears, were recorded (15). A score of 0 to 3, corresponding to 0=no, 1=mild, 2=moderate, 3= severe pain, was noted.

The adverse effects, if any, were noted. We injected sedative and opioid after propofol for get the most reliable response of patients. Anesthetic induction was continued with fentanyl 2 µg/kg and midazolam 0.03 mg/kg intravenously. Tracheal intubation was facilitated with 0.5 mg/kg atracurium and anesthesia was maintained with isoflurane 1.2%.

The patients were extubated after administering muscle relaxation antagonist. Patients were followed up, during first 6 hours and were assessed for pain, swelling or allergic reaction at the injection site of propofol by a blinded anesthesiologist.

For comparison of quantitative variables between the three groups, the ANOVA test and for qualitative variables the chi-squared test or Fisher’s exact test were used. The statistically significant level was $P<0.05$. All analyses were done using the SPSS software for Windows (16.0 Ver.).

Results

The study included 135 patients. Mean age of the patients was 43 ± 0 (16-80) years old, and 81 patients (60%) were male and 54 patients (40%) were women.

The overall incidence of pain was 82.2% in the saline group, 13.3% in the tramadol group, and 24.4% in the ondansetron group. Pain intensity was significantly less in patients receiving drugs for pretreatment than those receiving saline ($P=0.001$) (Figure 1).

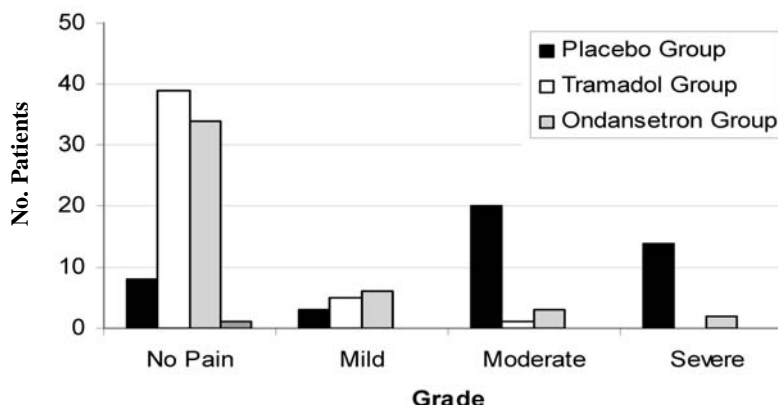


Figure 1. Comparison of the incidence of pain between three groups

* P value=0.330 (between pretreatment groups) SD=0

** P value=0.001 (between pretreatment groups and placebo group)

Four milligrams ondansetron, like 50 mg tramadol, significantly reduced the incidence of propofol injection pain. The efficacy of ondansetron in alleviating the incidence and severity of propofol injection pain was no different from tramadol ($P=0.330$).

No significant association was found between gender and pain ($P=0.855$), but pain in patients above 43 years old was significantly less than patients below 43 years old ($P=0.009$).

Discussion

Pain on injection of propofol (2,6-diisopropyl phenol) is considered to be a problem for the clinicians. The study reported incidence is 28% to 90% in adults and 28% to 85% in children (16).

Propofol has been commonly used for induction and maintenance of anesthesia, but pain of propofol injection can be extremely distressing to the patients (17). Up to now, the mechanism of pain due to propofol injection has been unclear. Propofol belong to the group of phenols and can directly irritate the skin, mucous membrane and venous intima and could immediately stimulate nociceptors and free nerve endings (8).

The concentration of propofol in solution associated with the injection pain. By its indirect action on the endothelium, it was considered that propofol activates the kallikrein-kinin system and releases bradykinin, through producing venous dilation and hyper permeability, which increases the contact between aqueous phase of propofol and free nerve endings, arises in delayed pain within half a minute (18-19). Recently, several studies have alluded that propofol had no effect on the concentration of bradykinin in plasma, compared with saline control group (20,21).

Yull *et al.*, have demonstrated that pain on injection of propofol may be related to release of local kininogens and that the nonsteroidal anti-inflammatory drugs (e.g. ketorolac) may have a role in reducing that pain (22).

Pain on injection of propofol has been reported since the initial studies (23) and is as yet, a limitation of this otherwise excellent IV anesthetic. Although it is not a serious complication, efforts are assumed to reduce the severity of the pain or discomfort.

Various pharmacological and non-pharmacological interventions have been done in investigate of elimination of propofol-induced pain (1,24,25).

Such as, lidocaine, cooling or diluting the propofol solution, and pretreatment with lidocaine, ephedrine, ondansetron, metoclopramide, nafamostat mesilate, opioids, thiopental, or ketamine (1,2,8,15,27-29). Pang

et al., showed that tramadol has local anesthetic effects (14). Tramadol has the same analgesic potency like pethidine and 1/10 that of morphine (6).

Ondansetron is commonly used as an antiemetic drug (30). In animal study, demonstrated that ondansetron administered intrathecally reduces the nociceptive responses of dorsal horn neurons (31). Ye *et al.*, showed that ondansetron is about 15 times more potent as local anesthetic than lidocaine, and this property probably contributes to its antiemetic action. Ondansetron also results in numbness when injected under the skin (7).

Ondansetron has the ability to block sodium channels. Peripheral 5-HT₃ receptors involve nociceptive pathways (7). Ondansetron binds to the opioid μ receptors in humans and exhibits agonist activity (32).

As a result of its multifaceted actions as a Na channel blocker, a 5-HT₃ receptor antagonist, and μ -opioid agonist, ondansetron may potentially be used to alleviate pain produced by a drug similar to propofol. Ondansetron is used at the time of induction of anesthesia for the prevention of post operative nausea and vomiting (PONV) (10-13).

The usual dose of ondansetron in adults is 4 mg (10,11). The main mechanism for the induction of pain with propofol injection has yet to be established; however, studies have shown that high concentrations of free propofol in the aqueous phase of an emulsion (33,34) and the lipid carrier (35) are associated with pain on injection. A kinin cascade has been suggested, which describes a slight delay before pain is experienced (18). The incidence of pain on injection of propofol using dorsal hand veins is reported to be 37.5% (5), 59.1% (12), and 46% (15). The use of forearm veins decreases the incidence of pain up to 2.5% (36).

Lidocaine pretreatment reduces the incidence of pain to 17.5% (36) and 19.5% (37). Other study have shown that mixed propofol and 1% lidocaine reduces the incidence of pain on injection significantly (38).

Our results demonstrated that the high incidence of pain or discomfort in 82.2% of cases, which was decreased to 24.4% after ondansetron pretreatment.

Also, we showed that there was no significant difference between the effectiveness of ondansetron and tramadol in decrease the pain on injection of propofol. In conclusion, ondansetron pretreatment provides a simple and safe method of reducing propofol injection pain with the advantage of preventing PONV and avoiding the administration of other drugs that may be undesirable in certain circumstances.

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