ISSN: 2091-2749 (Print)
2091-2757 (Online)

Efficacy of prophylactic intravenous ondansetron for attenuation of pain on propofol injection

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Submitted
25 Jan 2019

Accepted
24 Apr 2019

How to cite this article
Sujita Manandhar, Kishor Manandhar. Efficacy of prophylactic intravenous ondansetron for attenuation of pain on propofol injection. Journal of Patan Academy of Health Sciences. 2019Jun;6(1):31-36.

Abstract

Introductions: Propofol is a popular intravenous anesthetic agent. One disadvantage of propofol is pain on its injection which can be excruciating at times. Various agents and methods have been tried to attenuate this unpleasant effect. Ondansetron, primarily used as an antiemetic has also been studied to reduce it.

Methods: This randomized, prospective, double-blinded, placebo-controlled study was conducted on patients of either sex, American Society of Anesthesiologists (ASA) physical status I & II, undergoing elective surgeries requiring general anesthesia. The patients were randomly divided into ondansetron (A, received intravenous ondansetron 4 mg) and placebo (B, received equivalent volume of normal saline) groups. Manual occlusion of venous drainage was done at mid-arm by an assistant for 1 minute after which 25% of the calculated dose (2 mg/kg) of propofol (1% w/v in lipid base) was injected. Patients were asked by a blinded investigator to score the pain on injection of propofol on 4-point scale: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain and compared in between two groups. The $p<0.05$ was considered significant.

Results: There were 96 adult patients, 48 in each group of Ondansetron placebo. Pain on propofol injection was found significantly higher in the placebo group compared to the ondansetron group. (62.5% vs 35.4%). Most of the patients in the ondansetron group had mild pain only, whereas, a significant number of patients in the placebo group had higher degrees of pain on propofol injection.

Conclusions: Prophylactic intravenous 4 mg ondansetron is a safe and simple method of attenuating pain on propofol injection.

Keywords: general anesthesia, ondansetron, pain on propofol injection

Introductions

Propofol, a safe and smooth anesthetic inducing agent, has gained wide-spread popularity.[2] But pain during its injection, ranked an important problem in current practice of clinical anesthesia by American anesthesiologists[3-4], ranges from 28 to 90 percent in adults.[5-8] Several methods have been described to reduce it, but none of them completely attenuate it. Propofol belongs to the group of phenols that can irritate the skin, mucous membrane, and venous intima.[5-8] Ondansetron, a 5-HT3 receptor antagonist, commonly used antiemetic drug[9], binds to the opioid μ receptors in humans and exhibit agonist activity.[9] As a result of its multifaceted actions as a Na channel blocker, a 5-HT3 receptor antagonist, and μ opioid agonist, ondansetron can be used to alleviate pain produced by propofol.[10]

The present study was conducted to know the incidence of pain on propofol injection in our population which has been extensively studied in other countries and to analyze the efficacy of prophylactic ondansetron in attenuating it.

Methods

This prospective, double blinded, randomized, placebo-controlled comparative study was carried out at National Academy of Medical Sciences (NAMS) over the period of five months from August till December 2017. Adults 18-65 years of age of either sex, ASA physical status[1] I or II, undergoing elective surgeries requiring general anesthesia were included in the study. Exclusion criteria were patients with known allergy to study drugs, hemodynamic instability, who cannot communicate or speak, in whom IV access cannot be obtained in vein in the dorsum of hand, with diabetes mellitus and patients with autonomic or peripheral neuropathy. Ethical approval was taken from the Institutional Review Board of National Academy of Medical Sciences, Bir Hospital before conducting the study.

Adequate sample size was calculated based on the 60% incidence of pain on propofol injection reported by M Abdelnaser in 2016.[11] Assuming that ondansetron reduces pain incidence to 30% with alpha and beta value of 0.05 and 0.8 respectively, we would need at least 44 patients in each study group. Allowing for a dropout rate of 10%, 48 patients in each group were taken.

After pre-anesthetic check-up done by one of the researchers, all eligible subjects were explained about the study and informed written consent obtained. All study subjects were pre-medicated with oral diazepam (5 mg for patients weighing up to 50 Kgs and 10 mg for patients more than 50 Kgs) the night before surgery.

The patients were randomly divided into two groups, A (Ondansetron group) and B (Placebo group) by lottery method. Randomization was done by making the 96 slips of sealed envelope and every 48 slips had written A or B. All the envelopes were placed in a box.

On the day of surgery one slip was withdrawn from the box for each patient and the patient was assigned to the group accordingly. The drugs were prepared by the Anesthetist on duty not involved in the study according to the sealed randomization code, only accessible to him. Study drugs were prepared in 5 ml identical syringes to make clear solutions of either 4 mg Ondansetron diluted in normal saline to make 5 ml volume for patients in A(Ondansetron) group or 5 ml of normal saline for patients in group B. The Anesthetist on duty was requested to maintain confidentiality and record in the log book the administered drug to the patient according to the sealed randomization code in case de-blinding was necessary. Patient and the primary researcher anesthesiologist were unaware of the respective groups.

In the operation theatre, patients were attached to the standard monitors including pulse oximeter, noninvasive blood pressure, 3 lead Electrocardiogram and baseline parameters recorded. Intravenous access was

established with 18-G cannula in a suitable vein on dorsum of non-dominant hand without any local infiltration and preloaded with 15 ml/Kg of lactated Ringer solution over 30 mins. No analgesic drugs were given to the patient before injecting propofol.

The study drugs were then injected intravenously by the primary researcher anesthesiologist to the respective groups. Then manual occlusion of venous drainage was done at mid-arm by an assistant for 1 min. Then first 25% of Propofol (1% w/v in lipid base) at 2mg/kg dose was injected. Patients were asked standard questions about the pain according to the 4-point verbal categorical system and behavioral signs, Table 1.[14]

Table 1. Verbal rating score for the pain assessment for efficacy of prophylactic intravenous ondansetron for attenuation of pain on propofol injection

Score	Grade	Response to pain
0	None	No pain (negative response to question)
1	Mild	Pain without any behavioral signs, reported only in response to the question
2	Moderate	Pain reported in response to question and accompanied by behavioral sign (facial grimacing or withdrawal of hands or tears) and pain reported spontaneously without question.
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal and tears)

Thereafter, induction of anesthesia was continued with remaining dose of the propofol, and standard general anesthesia was commenced.

Data were represented as numerical (continuous and discrete) and categorical (nominal and ordinal) data and analysed using SPSS ver 16.0. Independent sample *t-test* were used for numerical data and Chi-square test for categorical data. P values <0.05 were considered statistically significant.

Results

Patient characteristics were comparable between the groups (Table 2). No patients were excluded from the study. Significantly fewer patients in the Ondansetron group had pain on propofol injection in comparison to the Placebo group (35.4% vs 62.5%), Table 3. Most of the patients in the Ondansetron group had mild pain on propofol injection compared to placebo, Table 3.

Table 2. Characterstics of patients in studying efficacy of prophylactic intravenous ondansetron for attenuation of pain on propofol injection

Variables	Group A (ondansetron)	Group B (placebo)	p Value
Age in years (mean±SD)	43.56±10.44	45±9.22	0.477
Gender:			
Male	25/48	28/48	0.538
Female	23/48	20/48	
Weight in Kg (mean±SD)	54.98±8.66	57.15±9.26	0.239
ASA:			
I	29/48	27/48	0.679
II	19/48	21/48	

Table 3. Incidence and severity of pain on propofol injection with or without prophylactic intravenous ondansetron for attenuation of pain

	Group A (Ondansetron)	Group B (Placebo)	p value
Pain on Propofol injection	17/48 (35.4%)	30/48 (62.5%)	0.008
Mild	14/48 (29.2%)	2/48 (4.2%)	0.001
Moderate	3/48 (6.2%)	16/48 (33%)	0.001
Severe	0	12/48 (25%)	0.000
No pain on Propofol injection	31/48 (64.6%)	18/48 (37.5%)	0.008

Discussions

In this study, we found incidence of pain due to Propofol intravenous injection was 62.5% and pretreatment with 4 mg of ondansetron significantly decreased the incidence of pain to 35.4%. Two other studies with study design similar to our study reported its incidence of 60%[11]and 55%.[19] Possible explanation for the immediate pain is from a direct irritant effect. Later, activation of the kallikrein-kinin system releasing bradykinin, causes local vasodilation and hyperpermeability, increases the contact between the aqueous phase propofol and the free nerve ending, resulting in pain on injection. This pain has a 10-20 seconds delayed onset.[7,24]

Pharmacological, non- pharmacological or a combination of both methods have been used in the attenuation of pain due to propofol injection. Some of them are pre-treatment or addition of lidocaine[13,15,20-22,24] pre-treatment with ondansetron,[11-13,15,17-19] opioids as fentanyl[22], administration of different formulas of propofol[16,23] that include long chain triglycerides (LCT) alone or medium-chain triglycerides (MCT) with LCT, mechanical interventions such as different infusion rates[24], venous occlusion[20,21], injection sites[24], temperature[14] have been used. Unfortunately, none of these have been proven to be ideal.

An intravenous bolus injection of propofol in the antecubital fossa was the only approach that caused no pain.[6,24] When administered intravenously in the dorsum of the hand the pain score and the number of patients experiencing pain was reduced significantly by mixing propofol with lignocaine. The incidence of pain on propofol injection would have been lower in our study if we had also chosen the veins in the antecubital fossa. However, the veins at the dorsum of hand are more convenient and accessible and is frequently used by anesthesiologists as unintentional extravasations of occluded IV lines in the elbow may go unnoticed. Slowing the rate of injection caused the greatest discomfort.[24] When propofol is injected mid-stream into the lumen of the vein, the larger diameter of and faster flow rate will minimize the extent of propofol coming into contact with the sensitive endothelial wall.[6] Even when propofol was injected in veins of the dorsum of hand without any pre-treatment, the incidence and severity of pain were significantly reduced when propofol was administered at a temperature of 4°C.[14] We could not control the temperature of propofol in our study and patients received propofol at room temperature which may affect the incidence and severity of pain on propofol injection. However, one systematic review and meta-analysis showed that cold propofol (4˚C), propofol at room temperature, and modifying the speed of the intravenous carrier fluid were non-effective interventions for reduction of pain on propofol injection.[6] This study also showed that pre-treatment with 4 mg of ondansetron significantly decreased the incidence of pain on propofol injection to 35.4%.

A similar study to ours showed significant reduction in the incidence of pain on Propofol injection in the ondansetron group from 60% to 26.7% and lesser pain scores with the pretreatment of 4 mg IV ondansetron.[11] Similarly, in another study, the incidence of pain was significantly reduced on propofol injection in ondansetron group vs control (from 55% to 25%) with severe pain significantly reduced in the ondansetron group (32.5% vs 7.5%).[19] The results of both of these studies, with similar study design as ours, are consistent with our findings. In our study also, most of the patients in the Ondansetron group had mild pain and only three of them complained of moderate pain, whereas, a significant number of patients in the Placebo group had higher degrees of pain on propofol injection, including 25% with severe pain. A study done in 2012 showed that ondansetron pretreatment significantly decreased the incidence of propofol injection pain from 82.2% to 24.4%.[18] Similar to our study, in these studies, propofol has been given on the veins of dorsum of hand and tourniquet applied after the injection of study drugs. The direct anesthetic effect of ondansetron achieved by venous occlusion, may have blocked the nerve

fibers responsible for transmission of pain resulting from direct irritation of the blood vessel walls by propofol.[10] Furthermore, numerous studies[11,18-21] have shown that a combination of drug and non-drug technique such as venous occlusion before drug injection is an effective intervention in reducing the pain on propofol injection.

Some of our limitations are that factors affecting the incidence of pain as speed of injection, temperature of propofol etc. could not be controlled. Pain, a subjective entity can result in a high chance of biased assessment. Various factors such as ethnic groups, enrolled subjects level of education etc. must be considered.

Conclusions

Prophylactic intravenous ondansetron (4 mg) is a safe and simple method of reducing pain on propofol injection.

Acknowledgements

We would like to express our sincere thanks to National Academy of Medical Sciences, Mahabouddha, Kathmandu for grant.

Funding

Funding was obtained from National Academy of Medical Sciences, Nepal.

Conflicts of Interests

None

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