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SCIENTIFIC ARTICLE

Ondansetron reducing pain on injection of etomidate: a controlled randomized study☆

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Abstract
Introduction: Etomidate causes pain when injected intravenously. In this study we sought to determine if pretreatment by ondansetron reduces the pain on injection of etomidate.
Methods: In this randomized, double blinded, placebo-controlled clinical trial, 20 patients of both sexes aged between 18 and 50 years of American Society of Anesthesiologists (ASA) physical status class I or II, whom were candidates for various elective surgical procedures and need more than one intravenous access were enrolled in the study. On arrival to the operating room two 22 gauge cannulas were inserted into veins on the dorsum of both hands. Following the infusion of 100 mL normal saline into both intravenous lines, using an elastic band, venous drainage of hands was occluded at midarm. The patients were administered 8 mg (2 mL) of ondansetron into one hand and 2 mL of 0.9% saline into the other hand at the same time. The elastic band was removed after 1 min and 2 mg (1 mL) of etomidate was administered at the same rate simultaneously into intravenous lines. The patients were asked to give a score of pain based on a verbal analog scale (VAS) to each hand.
Results: A total number of 20 patients were studied (male = 55%, female = 45%). The mean age of the participants was 37.5 ± 13.1 years old and the mean weight was 67.7 ± 7.3 kg. The mean VAS for injection pain of etomidate after pre-administration of intravenous ondansetron was 1.5 ± 1.2 which was lower compared to pre-administration of placebo (3.2 ± 2.8, $p < 0.05$).
Conclusion: This study illustrates that pre-treatment with intravenous ondansetron significantly reduces the pain on injection of etomidate.

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Introduction

Various agents have been used for intravenous induction of anesthesia, yet some of the side effects induced by different drugs limit their use.[1]

Etomidate is one of the popular intravenous anesthetic agents, which can be administered during induction of general anesthesia or sedation for short procedure.[1] Propylene glycol formulated etomidate may damage vascular endothelium and produce pain.[2] Etomidate is famous for its cardiovascular stability, nevertheless injection pain and postoperative vomiting are two unpleasant adverse effects attributable to this drug.[3]

The broad distribution of five hydroxytryptamine (5-HT3) receptors in human body has provided the basis for investigation of ondansetron, as a selective serotonin 5-HT3 receptor antagonist in novel applications, although the results have not always been consistent.[4,5]

The primary outcome of the present study was to determine the effect of ondansetron on prevention of injection pain caused by etomidate during induction of anesthesia.

Methods

Ethics

This trial was reviewed and approved by the Institute of Ethical Committee and Iranian Registry of Clinical Trials (IRCT ID: IRCT201106125140N4).

The study protocol was approved by the Institutional ethics committee of Tehran University of Medical Sciences. Ethical approval for this study (Ethical Committee N° 91/د/201/22501) was provided by the Ethical Committee of Tehran University of Medical Sciences (Chairperson Prof. Sh. Akhondzade) on 15 January 2013. An informed written consent was obtained from all the participants.

Patient's population

In this randomized, double blinded, placebo-controlled clinical trial, 20 patients of both sexes aged between 18 and 50 years of American Society of Anesthesiologists (ASA) physical status class I or II, who were candidates for various elective surgical procedures requiring more than one intravenous access lines were enrolled in the study.

Exclusion criteria consisted of patients with a history of thrombophlebitis or vascular disease, chronic pain, diabetes mellitus, history of tumors or burns in either hands, history of addiction or any contraindications to injection of ondansetron or etomidate.

In the preoperative visit the night before surgery all the patients were thoroughly explained the visual analog scale (VAS) for pain (0 = no pain, 10 = most severe pain). No premedications were administered.

Intervention

On arrival to the operating room, all patients were monitored with an electrocardiogram (ECG), noninvasive blood pressure and pulse oximetry. All the required drugs were prepared into opaque syringes by an anesthetist who was not involved in either the administration of drugs to patients or the patients' assessment; thus, both the anesthesiologist and the patients were blinded to patients groups.

Two 22 gauge cannulas were inserted into the veins on the dorsum of both hands. One hundred millimeters of saline was administered over 10 min from each of the cannulas. Using an elastic band as a tourniquet, venous drainage of both hands was occluded midarm. Eight milligrams (2 mL) of ondansetron was administered from one hand and 2 mL of 0.9% saline from the other hand at the same time. The elastic band was removed after 1 min and 2 mg (1 mL) of etomidate was administered at the same rate simultaneously at both hands. The patients were asked to give a score from 0 to 10 (0 = no pain and 10 = most severe pain) to each hand. Adverse effects were also recorded. The choice for the technique used for induction of anesthesia was left for the anesthesiologist to make based on every individual. Endotracheal intubation was facilitated with 0.5 mg kg^{-1} atracurium. After tracheal intubation, anesthesia was maintained by isofluran and N_2O (50%); 0.1 mg kg^{-1} atracurium and 1 μg kg^{-1}. Fentanyl were administered half hourly. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7–5.3 kPa).

Statistics

It was estimated that a sample size of 20 patients (40 hands) would be sufficient to detect a 3 score difference in pain on injection of etomidate, estimating a SD of 3.5, power of 95% and significant level of 0.05.

Statistical analysis of the results was performed using SPSS for windows, release 17.5 (SPSS Inc.). The intensity of pain was analyzed by two sample *t*-test. *p*-Value <0.05 was considered statistically significant. The power of study was considered 20%.

Results

Three patients were deeply sedated after injection of etomidate and unable to answer any questions. We replaced these three patients with new cases. A total number of 20 patients were enrolled in the study (male = 55%, female = 45%). The mean age of the participants was 37.5 ± 13.1 years and the mean weight was 67.7 ± 7.3 kg. The mean VAS for injection pain of etomidate after pre-administration of intravenous ondansetron was 1.5 ± 1.2 which was lower compared to pre-administration of placebo (3.2 ± 2.8, $p < 0.05$). Six patients developed urticaria following administration of ondansetron and before etomidate administration. No life threatening or major complications were observed.

Discussion

In this study the effect of intravenous ondansetron on injection pain of etomidate was evaluated. It was observed that administration of ondansetron prior to etomidate reduces the injection pain significantly.

Ondansetron has been shown to bind to opioid μ-receptors in humans and possess agonist activity.[6] Five hydroxytryptamine receptors are involved in the nociceptive

pathways. Five hydroxytryptamine receptors play a pronociceptive role and mediate descending excitatory controls that allow spinal neurons to fully code peripheral stimuli. Ondansetron decreases chronic benign neuropathic pain, this effect seems to be produced by an action on the neurons in the spinal cord that code and transmit peripheral nociceptive stimuli.[7]

Five hydroxytryptamine receptors are also a target for local anesthetics. The ability of ondansetron to block sodium channels and 5-HT3 receptor has put forward the hypothesis that ondansetron possesses antinociceptive properties probably in a similar way to local anesthetics. Although local anesthetics contain hydrophilic and hydrophobic structures separated by an intermediate amide or ester linkage, a structure which ondansetron does not have.[8,9]

Reducing injection pain of intravenous anesthetics has been the subject of various studies. Many drugs have been previously used to attenuate injection pain of propofol and rocuronium. Lidocaine or fentanyl with local anesthetic and sedative properties are the most commonly used drugs.[10–13] When compared to tramadol, ondansetron was equally effective in preventing pain of propofol injection, holding the analgesic properties of ondasetron, and was superior due to prevention of post operative nausea and vomiting.[14] Metoclopramide, and flurbiprofenaxetil, granisetron and ketamine effect on attenuating pain on injection have all been previously studied.[15–19]

Quantification of pain is a great challenge to researchers. Visual analog scale is one of the most popular methods used for pain assessment, but it is subjective and is difficult to evaluate quantitatively or statistically. Reported pain levels by individuals using VAS are based on every individuals pain threshold, which is unknown, making the whole results defective when compared between individuals. Not only a different definition of pain exists in different cultures around the world but also individual variability exists in perception of pain. Even every individual's pain threshold may change based on the underlying emotional state and environmental situation in which the pain is assessed.

Therefore, when pain is studied between different individuals, from different regions and in different conditions the results are neither trustworthy or dependable nor consistent. A ''Pain Vision'' system has been recently proposed for quantitative assessment of pain caused by the removal of adhesive wound dressing materials which takes into account every patient's pain threshold.[20]

We believe that in this study a new way of pain assessment has been put forward. In this method, every individual's hand is used as the case and control groups for pain perception, therefore reducing or even eliminating the mentioned intervariability in pain perception and confounding factors. In our previous work in which we assessed the effect of dexamethasone on injection pain of diazepam hydrochloride,[21] we used the this method too.

It should be noted that to our knowledge in all the previously injection pain assessment studies the method used to assess pain was different to our study and pain on injection was assessed between different individuals. This could lead to less reliable results.

We propose the method used in this study as a novel and effective way of assessing injection pain of various drugs. We are currently conducting a series of clinical trials, using the mentioned method, evaluating the effect of ondansetron and granisetron on the pain on injection of etomidate and propofol.

The question that what dosage of ondansetron is required to prevent injection pain of various drugs remains unanswered. Urticaria which developed in 6 patients was the negative aspect of ondansetron administration, although this was very short lasting and was probably related to the preservatives used and no major complication occurred in any of the individuals.[2] It should also be noted that ondansetron's antiemetic effect can help attenuate the postoperative nausea and vomiting effect of etomidate. We could not measure this variable because all the patients were administered ondansetron and we had no control group.

In conclusion, the result of this study demonstrated that ondansetron could effectively reduce pain on injection of etomidate.

Conflicts of interest

The authors declare no conflicts of interest.

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