



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
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SCIENTIFIC ARTICLE

Comparison of granisetron and lidocaine on reducing injection pain of etomidate: a controlled randomized study



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Received 6 July 2015; accepted 4 April 2017

Available online 27 June 2017

KEYWORDS

Granisetron;
Lidocaine;
Etomidate;
Pain

Abstract

Background and objectives: Reducing pain on injection of anesthetic drugs is of importance to every anesthesiologist. In this study we pursued to define if pretreatment by granisetron reduces the pain on injection of etomidate similar to lidocaine.

Methods: Thirty patients aged between 18 and 50 years of American Society of Anesthesiologists physical status class I or II, whom were candidates for elective laparoscopic cholecystectomy surgery were enrolled in this study. Two 20 gauge cannulas were inserted into the veins on the dorsum of both hands and 100 mL of normal saline was administered during a 10 min period from each cannula. Using an elastic band as a tourniquet, venous drainage of both hands was occluded. 2 mL of granisetron was administered into one hand and 2 mL of lidocaine 2% at the same time into the other hand. One minute later the elastic band was opened and 2 mL of etomidate was administered to each hand with equal rates. The patients were asked to give a score from 0 to 10 (0 = no pain, 10 = severe pain) to each the pain sensed in each hand.

Results: Two patients were deeply sedated after injection of etomidate and unable to answer any questions. The mean numerical rating score for injection pain of intravenously administered etomidate after intravenous granisetron was 2.3 ± 1.7 , which was lower when compared with pain sensed due to intravenously administered etomidate after administration of lidocaine 2% (4.6 ± 1.8), $p < 0.05$.

Conclusion: The result of this study demonstrated that, granisetron reduces pain on injection of etomidate more efficiently than lidocaine.

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PALAVRAS-CHAVE

Granisetrona;
Lidocaína;
Etomidato;
Dor

Comparação de granisetrona e lidocaína na redução da dor causada pela injeção de etomidato: estudo randômico e controlado

Resumo

Justificativa e objetivos: A redução da dor causada pela injeção de anestésicos é importante para todos os anesthesiologistas. Neste estudo buscamos definir se o pré-tratamento com granisetrona reduz a dor causada pela injeção de etomidato de forma semelhante à lidocaína. **Métodos:** Trinta pacientes com idades entre 18 e 50 anos, estado físico ASA I ou II (de acordo com a classificação da Sociedade Americana de Anesthesiologistas) e candidatos à colecistectomia laparoscópica eletiva foram incluídos neste estudo. Duas cânulas de calibre 20 foram inseridas nas veias do dorso de ambas as mãos e 100 mL de soro fisiológico foram administrados durante 10 minutos através de cada cânula. Usando um torniquete elástico, a drenagem venosa de ambas as mãos foi ocluída. Granisetrona (2 mL) foi administrado em uma das mãos e lidocaína a 2% (2 mL) na outra mão ao mesmo tempo. Após um minuto, o torniquete foi liberado e 2 mL de etomidato foram administrados em velocidade igual a cada uma das mãos. Solicitamos dos pacientes uma classificação de 0 a 10 para a dor sentida em cada uma das mãos (0 = sem dor, 10 = dor intensa).

Resultados: Dois pacientes estavam profundamente sedados após a injeção de etomidato e, portanto, incapazes de responder a qualquer pergunta. O escore médio de classificação da dor à injeção de etomidato administrado por via endovenosa após granisetrona intravenosa foi de $2,3 \pm 1,7$, o que foi menor em comparação com a dor sentida à administração intravenosa de etomidato após a administração de lidocaína a 2% ($4,6 \pm 1,8$), $p < 0,05$.

Conclusão: O resultado deste estudo demonstrou que granisetrona reduz a dor causada pela injeção de etomidato com mais eficácia que lidocaína.

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Introduction

Etomidate is an almost popular intravenous anesthetic agent, with almost unique hemodynamic profile following IV administration of it, as usually there is no hemodynamic change, so etomidate was considered for thermodynamically unstable patients. Etomidate is formulated in propylene-glycol therefore following intravenous injection, it may produce damages in vascular endothelium and so produces pain.¹ Considering the importance of using etomidate to produce a smooth induction of general anesthesia without any significant hemodynamic change, especially in cases with cardiovascular disorders or head trauma, prevention of pain on injection of etomidate seems to be logical.

To achieve this goal, many pretreatment by various drugs such as lidocaine, dexamethasone and magnesium sulphate were tested.^{2,3} Lidocaine significantly reduces the incidence and severity of pain on injection of anesthetic drugs.⁴

Granisetron is a selective inhibitor of Type 3 serotonergic (5-HT₃) receptors that has been used as an antiemetic and antinauseant for cancer chemotherapy patients. The broad distribution of five hydroxyl-tryptamine (5-HT₃) receptors in human body has provided the basis for investigation of granisetron, as a selective serotonin 5-HT₃ receptor antagonist in novel applications. Serotonergic receptor antagonists have been used to decrease pain on injection of some anesthetic agent with variable results.⁵⁻⁷ Probably inhibition of Type 3 serotonergic receptors can reduce the pain on injection of intravenously administered drugs.

In present study, it was hypothesized that granisetron can reduce pain on injection of IV etomidate similar and even more than lidocaine.

The effect of pretreatment by IV granisetron on pain of induction of etomidate was considered as primary outcome.

Methods

This trial was reviewed and approved by the Institutional Ethics Committee of Tehran University of Medical Sciences and was registered at Iranian registry of clinical trial (IRCT201411025175N19). An informed written consent was obtained from all the participants.

In this randomized, double-blinded, clinical trial, 30 American Society of Anesthesiologists (ASA) physical status class I patients aged between 25 and 60 years, who were candidates for elective laparoscopic cholecystectomy surgery requiring more than one intravenous access line were enrolled. Patients with a history of any neurological disease, chronic pain syndrome, thrombophlebitis or vascular disease, advanced systemic disorders such as diabetes mellitus and any contraindications of study protocol drugs, and addicted patient, were not enrolled in study. Exclusion criteria consisted of patients who dispensed with laparoscopic cholecystectomy surgery or patients who became deeply sedated before giving a score and patients whom veins were punctured more than once to gain. In the pre-operative visit in the night before surgery all the patients were thoroughly explained the Numeric Rating Scale (NRS)

for pain (0 = no pain, 10 = severe pain). No premeditations were administered.

On arrival to the operating room, all patients were monitored with an Electrocardiogram (ECG) noninvasive blood pressure and pulse-oximetry.

Two 20 gauge cannulas were inserted into the veins on the dorsum of both hands and 100 mL of normal saline was administered during a 10 min period from each cannula. Using an elastic band as a tourniquet, venous drainage of both hands was occluded. Two anesthesiologists, whom did not rate the pain scores, and where not aware of the drug solutions stood on each sides of the patients. An anesthesiologist who was not involved in the study prepared drug solutions. 2 mL of granisetron was administered into one hand and 2 mL of lidocaine 2% into the other hand at the same time. One minute later the elastic band was opened and 2 mL of etomidate was administered to each hand with equal rates at the same time. The patients were asked to give a score by the third anesthesiologist from 0 to 10 (0 = no pain, 10 = severe pain) to the pain sensed in each hand.

The choice for the technique used for induction of anesthesia was left for the patient's anesthesiologist. The patients as well as the anesthesiologist were unaware of the nature of the intervention drugs, thus, both the anesthesiologist and the patients were blinded to patients groups. Arbitrarily, we coded the drugs as AB (A for left hand and B for right hand) or BA (B for left hand and A for right hand). Using a randomly generated computer code, 32 patients were allocated to receive AB or BA in 4 blocks of 6 and 2 blocks of 4.

Based on previous works and paired study design, 30 pairs of hand would be sufficient to detect 50% reduction in percentage of NRS considering two sided $\alpha = 0.05$, 80% power, and 10% drop out. It was estimated that a sample size of 30 patients would be sufficient to comparison a reduction of pain score on injection of etomidate between granisetron and lidocaine.

Statistical analysis of data was performed using SPSS for windows, released 17.5. The intensity of pain was analyzed by paired *t* test; $p < 0.05$ was considered significant.

Data were analyzed with Software Package for the Social Sciences (SPSS, version 17.5). Normality of data was checked as needed. Paired *t*-test was used to compare NRS between right and left hands and McNemar–Bowker Test was used to compare categorized NRS between two hands.

Results

A total of 32 patients were enrolled in the study. Two patients were deeply sedated after injection of etomidate and unable to answer any question. The data about the patients and surgery are in [Table 1](#).

The mean NRS for injection pain of intravenously administered etomidate after intravenous granisetron was 2.3 ± 1.7 , which was lower when compared with pain sensed due to intravenously administered etomidate after administration of lidocaine (4.6 ± 1.8), $p < 0.05$. This statistically significant difference was still observed, when patients were stratified according to gender.

Table 1 Demographic data of the patients.

| | |
|------------------------------|-------------|
| Age (years) | 34.5 ± 10.1 |
| Sex (F/M) | 15/15 |
| Weight (kg) | 79.3 ± 11.2 |
| Height (cm) | 173.4 ± 8.2 |
| ASA (I/II) | 18/12 |
| Duration of surgery (min) | 108 ± 28.9 |
| Data presented as mean ± SD. | |

Discussion

In this study the effect of granisetron and lidocaine 2% on reducing the pain on injection of etomidate was compared. It was observed that administration of granisetron prior to etomidate reduces pain on injection of etomidate more efficiently than lidocaine.

For nearly a decade the current team of authors has been working on the effect of pretreatment of various drugs on pain on injection of intravenous drugs. A wide range of drugs such as dexamethasone, metoclopramide, ephedrine have been tested with different results.^{8–10} Dexamethasone and metoclopramide pretreatments were shown to be effective in reducing the severity of pain on injection of diazepam. It was demonstrated that small doses of ephedrine also showed promising results in attenuating the pain of injection. The fact that 5-HT₃ receptors are located in the peripheral and central nervous system was the rational for using ondansetron for the previous study and to pursue more studies on the actual effects of 5-HT₃ receptor antagonists. 5-HT₃ receptor antagonists also possess antinociceptive properties, so they can decrease pain in a similar way to local anesthetics. In an earlier study it was shown that ondansetron reduces pain on injection of etomidate effectively¹¹ which was congruent with the hypothesis that 5-HT₃ receptor antagonists are the near to precise class of drugs for reducing pain on injection.

Granisetron is a specific 5-HT₃ receptor antagonist that abolishes allodynia and hyperalgesia.^{12,13} Granisetron can treat emesis induced by chemotherapy and it seems this effect is equivalent to, or better than, that of ondansetron.¹⁴

Other studies have also been undertaken with the goal of reducing pain on injection of anesthetic drugs. Recently, granisetron has been shown to be more efficient in attenuating pain on injection of propofol compared to magnesium sulfate and nitroglycerine.¹⁵ The mechanism of granisetron in reducing pain on injection of propofol is not completely known, lidocaine is a peripheral local anesthetic that attenuates the afferent pain pathway rather than a central analgesic effect, similar to the mechanism of ondansetron.¹⁶ Ondansetron exhibits the properties of a local anesthetic and relieves pain on injection of propofol without any adverse effects.^{17,18} The effect of ondansetron, lidocaine, tramadol, and fentanyl have all been previously studied in decreasing intensity of rocuronium injection pain.^{19,20} In another study effect of ondansetron has been compared with lidocaine on pain intensity after rocuronium and propofol injection.²¹

Quantification of pain is a great challenge to researchers. One of the most popular methods used for pain assessment

is NRS, but it is subjective and is difficult to compare it between different subjects. Reported pain levels by individuals using NRS are based on every individual's pain threshold, which is unknown, making the whole results faulty 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 be altered based on the underlying emotional state and environmental situation in which the pain is assessed. 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.²²

In this study an almost new way of pain assessment, which has been used in previous studies of the same authors. In every individual, each of hands are used as a case, we administered the lidocaine in one hand and the granisetron in another hand and one person scored pain in each hand at the same time. We believed that in this way, many of confrontational factors are removed from the study. In our previous work in which we assessed the effect of ondansetron on injection pain of etomidate, one of the individual's hand was again used as a case and another hand was used as control group.¹¹

To our knowledge in nearly all of previous injection pain assessment studies the method used to assess pain was different to our study and pain on injection was assessed between different individuals. We believe that by this technique, our results are more reliable.

The negative aspect of lidocaine or granisetron was not measured, because all the patients were administered both lidocaine and granisetron and there was not any control group. Although the postoperative nausea and vomiting effect of etomidate was not measured. These can be considered as limitations of this study.

In conclusion, the result of this study demonstrated that, granisetron reduces pain on injection of etomidate more efficiently than lidocaine.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

The authors declare that Tehran University of Medical Sciences has funded this study.

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