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Oxycodone for prevention of etomidate-induced myoclonus: a randomized double-blind controlled trial

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Abstract

Objective: This study was performed compare the effectiveness of oxycodone and fentanyl in reducing the incidence and severity of etomidate-induced myoclonus.

Methods: In total, 162 patients with an American Society of Anesthesiologists physical status of I or II were assigned at random to three groups. Patients assigned to Group O received 0.1 mg/kg of oxycodone (n = 54), those assigned to Group F were given 1 μg/kg of fentanyl (n = 54), and those assigned to Group S were given an equal volume of saline intravenously 2 minutes prior to administration of 0.3 mg/kg of etomidate (n = 54). The incidence and severity of myoclonus was evaluated 2 minutes after etomidate administration. The patients' vital signs, coughing, nausea, dizziness, and other related adverse reactions were also recorded.

Results: The incidence of myoclonus was significantly lower in Group O (0.0%) than in Group F (31.5%) and Group S (72.2%); the intensity was also lowest in Group O. All patients in each group had stable cardiovascular profiles.

Conclusions: Intravenous injection of 0.1 mg/kg of oxycodone 2 minutes prior to etomidate is more effective in preventing etomidate-induced myoclonus during general anesthesia than is 1 μg/kg of fentanyl.

Keywords

Anesthetics, etomidate, myoclonus, oxycodone, fentanyl, general anesthesia

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Introduction

Etomidate, a nonbarbiturate hypnotic drug, is currently used to induce anesthesia while maintaining a stable cardiovascular profile.[1] However, induction of anesthesia with etomidate results in dose-dependent myoclonus in 50% to 80% of patients without prevention.[2] Myoclonic movements can lead to patient discomfort, pose a challenge in patients with partial cardiovascular reserves, and increase the risk of aspiration in patients with a full stomach. Myoclonus can also increase intraocular pressure and cause problems in patients undergoing open eye surgery.[3]

Opioids have been used to prevent myoclonus induced by etomidate. However, using opioids can result in unwanted adverse effects such as apnea.[4] Preadministration of 100 μg of fentanyl 5 minutes before injection of etomidate can reduce the incidence of myoclonus by one-half, but the incidence of apnea is increased.[5] In contrast, other opioids such as oxycodone can excite both κ and μ G-protein-coupled receptors.[6] The etomidate-induced myoclonus may be considered a type of seizure.[7] As an agonist of κ opiate receptors, oxycodone can limit these seizures.[8] However, no comparative studies showing whether oxycodone or fentanyl is a better option in the prevention of etomidate-induced myoclonus have been reported. This study was designed to evaluate the effect of oxycodone pretreatment on the incidence and severity of etomidate-induced myoclonus during the induction of general anesthesia compared with fentanyl.

Methods

Trial registration and ethics

The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized controlled clinical trials were followed in this study.[9] This study was registered in the Chinese Clinical Trial Registry (ID: ChiCTR-IPC-16009154) on 4 September 2016. Ethical approval for the study (2015-3-1) was provided by the Ethics Committee of Jiangning Hospital Affiliated to Nanjing Medical University on 1 March 2015. All patients involved provided informed consent prior to the study.

Participants

Patients undergoing elective operations by general anesthesia in our institution were enrolled from 2 March 2015 to 31 December 2016. Patients with drug allergies or neurological diseases and those who had received sedatives, analgesics, or alcohol within the previous 24 hours were excluded.

Study design

Patients were randomly assigned to three groups. Patients in Group O received 0.1 mg/kg of oxycodone, those in Group F received 1 μg/kg of fentanyl, and those in Group S received an equal volume of saline. A computer-generated table of random numbers was used to randomize the patients into separate groups, and both patients and researchers were blind to the group identity of each patient. All drugs were prepared using black 10-mL syringes by an anesthesiologist who remained independent from the study.

Interventions and outcome measures

To decrease upper airway secretions, 0.5 mg of atropine was injected intramuscularly 30 minutes prior to patient arrival in the operating room. Patients were given 0.9% saline at a rate of 50 mL/hour by intravenous puncture with a 20-gauge needle on the dorsum of the right forearm prior to administration of anesthesia. Heart rate, noninvasive blood pressure, pulse oximetry [blood oxygen saturation (SpO_2)], and

electrocardiography were monitored throughout the procedure.

After preoxygenation for 3 minutes, the pretreatment drug was injected for at least 30 seconds. Two minutes after injection, anesthesia was induced by administration of a lipid formulation of etomidate (Etomidate-Lipuro, 0.3 mg/kg; B. Braun Medical, Mumbai, India) for a duration of 30 s. The presence and intensity of myoclonus were evaluated 2 minutes after administration of etomidate, and vecuronium (0.1 mg/kg) and remifentanil (target-controlled infusion mode with a target plasma concentration of 3.0 ng/mL) were then administered to facilitate tracheal intubation.

Myoclonus was evaluated by an anesthesiologist who was blinded to the patients' pretreatment drug and grouping. Myoclonic movements were divided into four grades according to their intensity: no myoclonus, mild myoclonus (slight movement in one part of the body, such as a finger or shoulder), moderate myoclonus (slight movement of two different muscles, such as the face or legs), or severe myoclonus (strong contracture of two or more muscles, such as rapid abduction of the limbs).[10]

Adverse effects were checked blindly by a separate anesthesiologist and included cough, dizziness, and nausea during the time from administration of oxycodone, fentanyl, or saline to the administration of etomidate. Heart rate, blood pressure, and SpO_2 were recorded once per minute throughout the study.

Justification of sample size and statistical analysis

According to previous studies,[2,10] the frequency of myoclonus in Group S was expected to be approximately 70%. Power analysis showed that a reduction rate of 30% with $\alpha = 0.05$ (one-tailed) and a 15% dropout rate within a power value of 90% could be detected with a sample size of at least 54 per group.

All statistical analyses were performed with SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation, and differences between groups were analyzed using mutual comparison after single factor variance analysis. The incidence and severity (mild, moderate, or severe) of myoclonic movements were considered categorized variables and analyzed using a chi-square (χ^2) test. For all data, a P value of <0.05 was considered statistically significant.

Results

In total, 162 patients (age 22–64 years, 82 men, 80 women) were enrolled in this study (Group O, n = 54; Group F, n = 54; Group S, n = 54). All participants had an American Society of Anesthesiologists (ASA) physical status of I or II. No participants were excluded from the study, and all patients' data were analyzed (Figure 1).

No significant differences in sex age, body weight, or ASA physical status were found among the three groups (Table 1).

The incidence of myoclonus was significantly lower in Group O (0.0%) than in Group F (31.5%) and Group S (72.2%) ($P < 0.001$). Additionally, the incidence of myoclonus was significantly lower in Group F than Group S ($P < 0.001$). Among all three groups, the intensity of myoclonus was lowest in Group O (Table 2).

There were no differences in the adverse effects (nausea, dizziness, and cough) among the three groups. No patients in any group experienced nausea. Only two patients from Group O experienced dizziness, one patient from Group F experienced dizziness, and one patient from Group F experienced coughing. No participants from Group S experienced any of these adverse effects (Table 3).

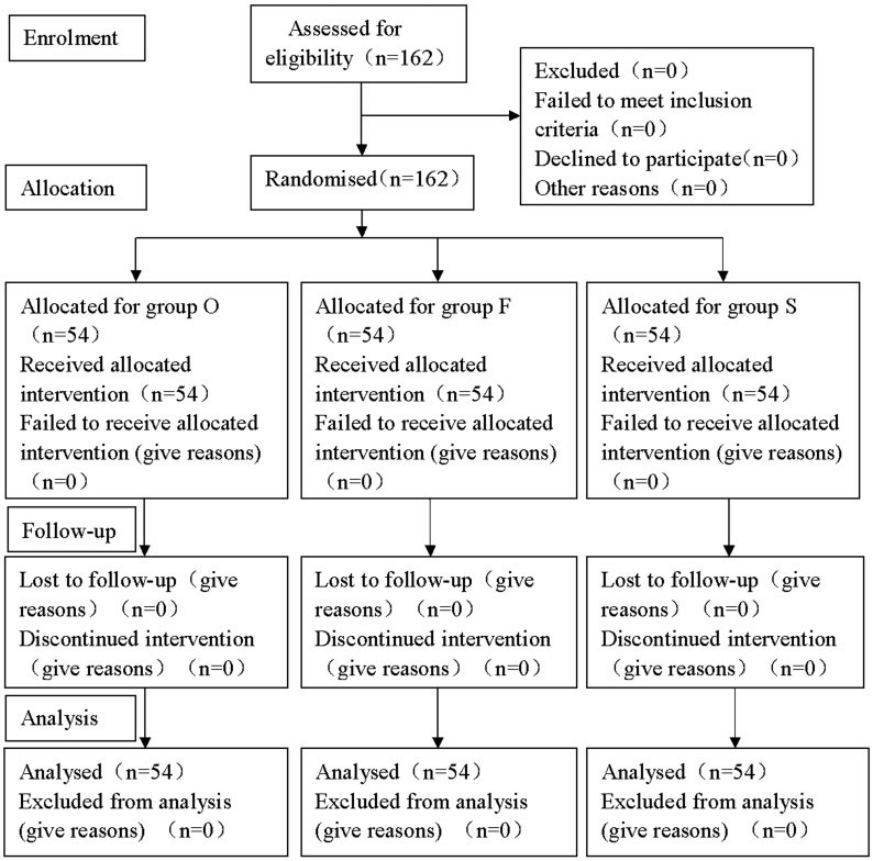

Figure 1. CONSORT flow diagram. In total, 162 patients were enrolled in this study. No patient was excluded from the trial, and all patients' data were analyzed. CONSORT, Consolidated Standards of Reporting Trials.

Table 1. Characteristics of patients in the three groups

	Sex (M/F)	Age (years)	Weight (kg)	ASA physical status (I/II)
Group O (n = 54)	28/26	46.4 ± 11.5	68.8 ± 9.5	21/33
Group F (n = 54)	29/25	45.4 ± 10.6	66.9 ± 9.1	24/30
Group S (n = 54)	25/29	48.3 ± 9.7	70.3 ± 8.2	23/31

Data are presented as mean ± standard deviation or number. There were no significant differences in patient characteristics among the three groups. M, male; F, female; ASA, American Society of Anesthesiologists.

The monitored SpO_2 exceeded 97% in all patients, and all showed stable cardiovascular profiles. No patients developed bradycardia or hypotension throughout the study.

Discussion

In this randomized, double blind, placebo-controlled trial, we used a sample size that was in accordance with our statistical method of estimating differences in

Table 2. Incidence and severity of myoclonic movements after etomidate injection in the three groups

	Myoclonus				Incidence (%)
	None	Mild	Moderate	Severe	
Group O (n = 54)	54[a]	0[a,b]	0[a,b]	0[a,b]	0[a,b]
Group F (n = 54)	37[a]	4	6	7	31.5[a]
Group S (n = 54)	15	10	12	17	72.2

Data are presented as number of patients. Compared with Group S, [a]$P < 0.001$ (χ^2 test); Compared with Group F, [b]$P < 0.001$ (χ^2 test).

Table 3. Number of adverse effects in the three groups

	Cough	Dizziness	Nausea
Group O (n = 54)	0 (0.0)	2 (3.7)	0 (0.0)
Group F (n = 54)	1 (1.9)	1 (1.9)	0 (0.0)
Group S (n = 54)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as number (%). The adverse effects (cough, dizziness, and nausea) occurring in patients from each of the three groups were similar.

myoclonic movements among groups. Fentanyl was selected as a positive control because of its common use as a preventative measure for myoclonus induced by etomidate.[5] Because the time from the intravenous injection of oxycodone and fentanyl to the onset of their effects is approximately 2 to 3 minutes, we administered oxycodone or fentanyl intravenously 2 minutes prior to treatment with etomidate. We continued to observe each patient for 2 minutes after intravenously injecting etomidate because previous reports have indicated that etomidate-induced myoclonus occurs 30 to 90 s after injection.[11] Previous studies have also shown that the analgesic efficacy of intravenous administration of fentanyl is approximately 50 to 60 times higher than that of oxycodone.[12,13] Therefore, it was difficult to select equipotent dosages of oxycodone and fentanyl. In our study, the dose of oxycodone (0.1 mg/kg) was obviously greater than that of fentanyl (1 μg/kg), but it was more effective at suppressing myoclonic movements without an increase in adverse reactions.

Many agents have been shown to reduce myoclonus with differing potencies, but the most effective compounds are opioids. In previous studies, intravenous administration of 1 μg/kg of fentanyl, 1 μg/kg of remifentanil, or 0.3 μg/kg of sufentanil 2 minutes prior to etomidate-induced anesthesia reduced the incidence of myoclonus to 28%, 29%, and 10%, respectively.[4,14] However, as the doses of opioids increase, the incidence of adverse effects such as cough, chest wall rigidity, and apnea also increase. Benzodiazepines can also reduce etomidate-induced myoclonus. In one study, a dose of 0.05 mg/kg of midazolam reduced the myoclonic movements from 77% to 17%.[15] Muscle relaxants such as atracurium have been shown to reduce the incidence of myoclonus from 66% to 15% at a low dose (20% of $ED_{95} \times$ kg, where ED_{95} is the dose required to produce 95% depression of twitch height).[16] Doses of 0.5 and 1 μg/kg of dexmedetomidine reduced the incidence of myoclonus from 63.3% to 36.7% and 30.0%, respectively.[17] However, pretreatment with 1 μg/kg resulted in significant adverse effects. Additionally, pretreatment with lidocaine (2%, 20 mg) reduced the incidence of myoclonus from 68% to 21%.[18] Finally, Un et al.[19] showed that the incidence of myoclonus can be reduced from 72% to 34% using magnesium sulfate at a plasma concentration of 2.48 mmol/L. However, none of the above-mentioned

drugs have been shown to have a higher potency than opioids.

Etomidate mainly produces anesthetic effects by acting on γ-amino butyric acid (GABA) receptors, but its specific mechanism of inducing myoclonus remains unclear. Lu et al.[20] considered that etomidate enhances the sensitivity of GABA neurons to the neural pathways associated with skeletal muscles, leading to the occurrence of some spontaneous neural impulses, which may result in myoclonus. Opioids can reduce the release of GABA and change the function of GABA receptors, which may be one of the mechanisms of preventing etomidate-induced myoclonus.[14] Studies have shown that myoclonic movements induced by etomidate are associated with seizures, which can be inhibited by activation of the κ opiate receptor.[7,8] In contrast to fentanyl, which activates only μ opiate receptors, oxycodone is a potent ligand for both κ and μ receptors. Therefore, it is possible that oxycodone decreases etomidate-induced myoclonus by modulation of the κ opiate receptor.

This clinical trial had several key limitations. Our main determination of the physiological outcome (incidence of myoclonus) could be viewed as a subjective measure. However, there were no other convenient and accurate indicators based on previous studies. Furthermore, the intensity of myoclonus was similar between Group F and Group S, which may be related to the sample size of the study. Finally, our analysis did not account for sex-related bias with regard to the differences in the incidence of myoclonus among the groups.

In summary, intravenous infusion of 0.1 mg/kg of oxycodone 2 minutes prior to the administration of etomidate appears to be more effective than pretreatment with 1 μg/kg of fentanyl in suppressing myoclonic movements during the induction of general anesthesia.

Authors' contributions

Wei Wang and Jie Lv designed the study, Qi Wang supervised the performance of the clinical trial, Wei Wang and Lei Yang analyzed the data, and Wei Wang and Wanyou Yu wrote the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The authors declare there is no conflict of interest.

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