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Pretreatment with Oxycodone Simultaneously Reduces Etomidate-Induced Myoclonus and Rocuronium-Induced Withdrawal Movements During RapidSequence Induction

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Background: Etomidate and rocuronium are often paired in rapid-sequence anesthesia induction. However, the effect of pretreatment with oxycodone on myoclonic and withdrawal movements has not been previously investigated. The aim of this study was to evaluate the effects of oxycodone on the incidence and severity of etomidate-induced myoclonus and rocuronium-induced nociceptive withdrawal movements during rapidsequence anesthesia induction.

Material/Methods: We randomly divided 120 patients into the saline group (group S) and the oxycodone group (group O) (n=60 in each group). Patients received 0.05 mg/kg oxycodone or saline intravenously 2 min before administration of 0.3 mg/kg etomidate. The occurrence and severity of myoclonus were assessed after administration of etomidate, then rocuronium was injected, followed by evaluation of withdrawal movements.

Results: The total frequency of involuntary movements following sequential administration of etomidate and rocuronium was significantly lower in Group O than in Group S (28.3% *vs.* 90%, p<0.001). The total frequency and grade 3 severity of myoclonus following etomidate injection in Group O was significantly lower than in Group S (25.0% *vs.* 63.3% for total frequency; 0 *vs.* 10 for grade 3 severity, *P*<0.001). The total frequency and grade 3 intensity of withdrawal movements were significantly less in Group O than in Group S (6.7% *vs.* 73.3% for total frequency; 0 *vs.* 11 for grade 3 intensity, *P*<0.001).

Conclusions: Oxycodone is effective for simultaneously preventing etomidate-induced myoclonus and rocuronium-induced withdrawal movements during general anesthesia induction.

MeSH Keywords: Epilepsies, Myoclonic • Etomidate • Oxycodone

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Background

Etomidate is a non-barbiturate hypnotic agent and rocuronium is an aminosteroidal non-depolarizing neuromuscular blocking agent [1,2]. Both drugs are widely used for induction of general anesthesia for their sedating and muscle relaxant effects, respectively. The combination of these 2 agents has the advantages of rapid onset of action and the low frequency of hemodynamic adverse effects [3,4]. Therefore, etomidate and rocuronium are often paired sequentially, especially in rapid-sequence anesthesia induction [4]. However, etomidate and rocuronium have severe adverse effects of myoclonus and withdrawal movements, respectively, and both are characterized by involuntary movement. The reported incidence of myoclonus caused by etomidate is as high as 50–80%, and rocuronium has been reported to cause withdrawal movements in 50–80% of patients when administered intravenously [5,6]. In addition to discomfort and secondary injuries, these adverse effects can also cause more serious problems in patients scheduled for emergency surgery under non-fasting condition, those with penetrating eye injuries, or with limited cardiovascular reserve [7,8]. Therefore, a variety of drugs, including opioids, have been investigated for their efficacy to counter myoclonus and withdrawal movements. Pretreatment with fentanyl or remifentanil has been shown to reduce myoclonus or withdrawal movements to some extent [9,10]. However, there have been few trials showing simultaneous suppression of these 2 adverse effects with a single pretreatment. Since etomidate and rocuronium are often paired in rapid-sequence anesthesia induction, the concept of suppressing myoclonus and withdrawal movement simultaneously with a single pretreatment is promising.

Oxycodone is a semi-synthetic opioid derivative and is generally indicated for the relief of moderate to severe pain [11,12]. As an opioid, oxycodone resembles morphine structurally and has a similar antinociceptive effect. However, it has different pharmacological profiles from μ-selective opioid receptors like morphine, fentanyl, remifentanil, or sufentanil; oxycodone acts as a κ opioid receptor agonist with a relatively low affinity for μ-opioid receptors [13,14]. The effectiveness of pretreatment with oxycodone on myoclonic and withdrawal movements has not been previously investigated. The aim of the present study was to test our hypothesis that pretreatment with oxycodone reduces the incidence and severity of etomidate-induced myoclonus and rocuronium-induced withdrawal movements during induction of anesthesia.

Material and Methods

Patients

This randomized, double-blind, placebo-controlled clinical trial was performed in the First Affiliated Hospital, Zhejiang University. After approval by the Medical Ethics Committee of the First Affiliated Hospital, Zhejiang University, eligible patients were approached for recruitment between August 2015 and October 2015. The study was registered prior to patient enrollment in the Chinese Clinical Trial Registry (*http://www.chictr.org.cn/*) with number ChiCTR-OOR-15006920, on August 8, 2015. The registry title is "Effects of oxycodone pretreatment on the adverse reactions during rapid-sequence induction with etomidate and rocuronium" and the principal investigator's name is Xiaoxia An. We enrolled 120 patients with American Society of Anesthesiologists (ASA) physical status I or II (aged 18–65 years) scheduled to receive elective surgeries under general anesthesia. Written informed consent was obtained from all patients prior to study initiation. Patients with neurologic diseases, severe diabetes mellitus, drug allergy, or those who received analgesics, sedatives, or opioids within the previous 24 h were excluded from the study.

Groups

Using a computer-generated randomizing table, patients were randomly assigned into 2 groups (60 in each group) to receive either oxycodone (oxycodone hydrochloride injection, 10 mg/ml, HAMOL Limited, Nottingham, UK) (0.05 mg/kg, Group O) or placebo (saline, Group S). Drugs were prepared in 5-ml syringes by an anesthesiologist who was not involved in induction of anesthesia.

Anesthesia and evaluations of myoclonus and withdrawal movements

All patients were fasting from midnight, and none were premedicated. Upon arrival at the operating room, an 18-gauge cannula was inserted into a dorsal vein of the hand, and lactated Ringer's solution was infused. Basic monitoring including electrocardiogram, pulse oximetry, invasive radial arterial blood pressure, and a standard bispectral index (BIS) was initiated before induction of anesthesia. After pre-oxygenation for 2 min, the pretreatment drug was given intravenously and patients were closely monitored for peripheral oxygen saturation and any signs of discomfort such as chest wall rigidity, coughing, or dizziness. At 2 min after the pretreatment, anesthesia was induced with 0.3 mg/kg etomidate (Etomidate-Lipuro, 2 mg/ml, B. Braun Melsungen AG) for 30 s. Myoclonic movements and time of onset of myoclonus after injection were observed by an anesthetist who was unaware of the nature of the pretreatment during the first 2 min following etomidate injection, and graded according to clinical severity. The intensity grades were as follows: 0=no myoclonus, 1=mild myoclonus (small movements in 1 body segment, such as finger or wrist), 2=moderate (slight movements in 2 or more muscle areas, such as face or shoulder), and 3=severe (intense movements in 2 or more muscle areas, such as sudden adduction of an extremity) [9]. Two minutes after etomidate administration (or until the termination of the myoclonus if the myoclonus persisted after 2 min),

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Table 1. Characteristics of patients in the oxycodone group (Group O) and saline control group (Group S).

Characteristic	Group O (N=60)	Group S (N=60)	P
Age (y)	53±9	52±10	0.764
Weight (kg)	62±10	63±11	0.783
Height (cm)	165±7	165±8	0.790
Gender (male/female)	23/37	24/36	0.852
ASA physical status (I/II)	39/21	38/22	0.852

Values are presented as mean ±SD.

0.6 mg/kg rocuronium (rocuronium bromide injection, 5 mg/ml, N. V. Organon) was injected over a 5-s interval, and intravenous fluid was continuously administered for 10 s. At the time rocuronium was being injected, withdrawal movements were evaluated by an anesthetist who was unaware of the nature of the pretreatment. The withdrawal movements were graded using a 4-point scale (grade 0=no movement, grade 1=movement at wrist only, grade 2=movements involving upper arm and shoulder of the injected arm, and grade 3=generalized movements or withdrawal in more than 1 extremity, cough, or holding of breath) [15]. Adverse effects of the drugs, such as headache, dizziness, nausea, and apnea were recorded after pretreatment. All data were recorded and assessed by an anesthesiologist who was blinded to study group assignment.

Statistics

Sample size was calculated with power analysis based on results that were previously published in patients undergoing etomidate or rocuronium induction; therefore, frequency of myoclonus and withdrawal movements in Group S was expected to be around 0.6. Power analysis indicated that a sample size of 48 per group yielded a 90% power to detect a reduction rate of 0.3 with α=0.05 (1–tailed). We factored in a 10–20% dropout rate and enrolled 60 patients in each group. Collected data were statistically analyzed using SPSS software (version 19.0, SPSS Inc., Chicago, USA). Continuous variables were described as mean±standard deviation and differences between groups were analyzed by using Student's t-test for normally distributed data. Categorized variables (e.g., sex and ASA class) were analyzed using the chi-square test. Frequencies of myoclonus and withdrawal movements were analyzed by the Mann-Whitney-Wilcoxon test. p<0.05 was considered to be statistically significant.

Results

Demographical characteristics and onset of myoclonus

During the study period, 120 participants were recruited and all of them completed the trial. The 2 groups were demographically comparable (Table 1). Myoclonus occurred 8–43 s after the end of etomidate administration, and there were no significant differences between Group O and Group C (15.00±7.58 *vs.* 18.87±10.80) (Table 2).

Table 2. Time to onset of myoclonus after etomidate injection.

	Onset of myoclonus after injection (s)	P
Group O	15.00±7.58	0.211
Group S	18.87±10.80	

Values are presented as mean ±SD.

Effect of oxycodone on total involuntary movements, etomidate-induced myoclonus, and rocuronium-induced withdrawal movements

The total frequency of involuntary movements following etomidate and rocuronium sequential administration was significantly lower in Group O than in Group S (28.3% *vs.* 90%, p<0.001) (Table 3). The total frequency of myoclonus was significantly lower in Group O than in Group S (25.0% *vs.* 63.3%, p<0.001). The numbers of patients with grade 3 severity of myoclonus were 0 in Group O and 10 in Group S (Table 4). In addition, the total frequency of withdrawal movements following rocuronium injections was significantly lower in Group O than in Group S (6.7% *vs.* 73.3%) (Table 5). No patients had a withdrawal score of 3 in Group O, as compared with 11 patients in Group S (Table 5). During the pretreatment period, no patients had decreased peripheral oxygen saturation, coughing, chest wall rigidity, or any other adverse effects, except that 3 patients in Group O felt mild dizziness.

Discussion

This study showed that single pretreatment with oxycodone (0.05 mg/kg), an opioid derivative, was effective in simultaneously reducing the incidence and the severity of etomidate-induced myoclonus and rocuronium-induced withdrawal movements.

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Table 3. The incidence of total involuntary movements following etomidate and rocuronium administration.

	Involuntary movements	None of involuntary movements	P
Group O (n=60)	17	43	0.000
Group S (n=60)	54	6	

Table 4. Frequency and severity of myoclonus after injection of etomidate.

Characteristic	Group O (N=60)	Group S (N=60)	P
0*	45	22	0.023
1*	10	22	0.059
2*	5	6	0.773
3*	0	10	0.002
Total frequency (%)	25.0	63.3	0.002

* Values are frequencies.

Table 5. Frequency and severity of withdrawal movements after injection of rocuronium.

Characteristic	Group O (N=60)	Group S (N=60)	P
0*	56	16	0.001
1*	3	9	0.098
2*	1	24	0.001
3*	0	11	0.001
Total frequency (%)	6.7	73.3	0.001

* Values are frequencies.

Etomidate is a non-barbiturate hypnotic agent and rocuronium is an aminosteroidal nondepolarizing muscle relaxant. A multicenter prospective surveillance on emergency intubations from 2002 to 2012 showed that among patients who received rapid sequential intubation with drug administration, etomidate was used in 91% of cases, and use of rocuronium was also rapidly increasing to up to 42% in 2010–2012 [4]. However, etomidate-induced myoclonus and rocuronium-induced withdrawal movements are still common problems, presenting with involuntary movement, and may cause severe distress in patients. In this study, the incidence of total involuntary movements following etomidate and rocuronium administration was as high as 90%. The incidence of myoclonus was 63.3% and that of withdrawal movements was 73.3% in the no pretreatment group, consistent with previous reports [6,7]. Clearly, simultaneous suppression of these 2 adverse effects continues to be a clinical challenge that prevents the wide use of combined etomidate and rocuronium during induction of anesthesia.

Although the exact pathogenic mechanisms for etomidate-induced myoclonus and rocuronium-induced withdrawal movements are not clearly established, many mechanisms had been proposed to explain both of them. Myoclonus after etomidate injection may be caused by temporary subcortical disinhibition, since a large dose of etomidate depresses cortical activity before it depresses subcortical activity [16]. The pathogenic mechanisms of withdrawal movements following rocuronium injection include direct activation of C-nociceptors by the non-physiological osmolality or low pH of the solution (pH 4) and release of endogenous mediators, such as bradykinin and histamine [17]. Therefore, suppression of myoclonus and withdrawal movements seems to involve both peripheral and central mechanisms. Since opioid receptors are not only distributed in the nervous system, but also throughout the body, including the vascular endothelium, use of opioids such as fentanyl, sufentanil, and remifentanil for the prevention of myoclonus or withdrawal movements has been widely reported in the literature [7,9,10]. Sinan et al. reported that pretreatment with fentanyl (1 μg/kg) or midazolam (0.03 mg/kg), or in combination with fentanyl (0.5 μg/kg) and midazolam (0.015 mg/kg), was effective in preventing myoclonus, as the incidence of myoclonus reduced from 85% (placebo group) to 40%, 70%, and 25%, respectively [9]. Pretreatment with sufentanil before etomidate also similarly decreased the incidence of myoclonus [7].

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Abu-Halaweh found that using a venous occlusion technique for 60 s, pretreatment with fentanyl and remifentanil was effective in preventing withdrawal movements caused by rocuronium injection in children and adolescents [10]. Surprisingly, no published data are available on simultaneous suppression of myoclonus and withdrawal movements induced by both drugs with a single pretreatment, even though this would be valuable in the rapid-sequence anesthesia induction by etomidate and rocuronium in some patients.

Oxycodone is a semi-synthetic opioid derivative and its analgesic action is mainly mediated by κ-opioid receptors [14]. He et al. reported that pretreatment with butorphanol (a κ opiate receptor agonist) reduced the incidence of etomidate-induced myoclonus from 79.6% (placebo group) to 13% [18]. Similarly, in the present study, we found that pretreatment with oxycodone was effective in reducing the incidence of myoclonus compared with placebo control, and none of patients in oxycodone group had severe myoclonus (grade 3). Furthermore, we found that the incidence and severity of rocuronium-induced withdrawal movements were significantly decreased when premedicated with oxycodone compared with that in the control group. It is known that κ opiate receptor agonists interact with a variety of neurotransmitter systems [18]. We speculate that the effects of oxycodone on opioids receptors, especially on κ-opioid receptors, are responsible for simultaneous reduction of myoclonus and withdrawal movements.

Choi et al. showed that pretreatment with a priming dose of rocuronium (0.06 mg/kg) 3 min before induction with etomidate significantly reduced the frequency of myoclonus by its neuromuscular block [19]. Rocuronium is characterized by a rapid onset of action; however, there are no reported studies that have investigated whether rocuronium can suppress a possibly delayed myoclonus and thereby result in lower rates when it was administered after etomidate in sequential anesthesia induction. In this study, we found that after 0.3 mg/kg etomidate, myoclonus occurred 8–43 s (mean 15–18 s) after the injection, perhaps because rocuronium injected after etomidate may not reduce the myoclonus, as the onset of myoclonus is relatively rapid.

There are 2 major limitations in this clinical trial. First, when we were testing 2 drugs sequentially, rocuronium was administered 2 min or longer after the injection of etomidate, rather than administered after loss of consciousness (as usual), so we cannot completely rule out the possibility that the extended acting time of etomidate might affect withdrawal movements following subsequent injection of rocuronium. Second, we did not investigate the optimal clinical dose of oxycodone on myoclonus and withdrawal movements, since none of previous studies evaluated its effect in pretreatment. Further studies are needed to determine the ideal dose of oxycodone under this condition.

Conclusions

In conclusion, we found that pretreatment with oxycodone is an effective method for prevention of etomidate-induced myoclonus and rocuronium-induced withdrawal.

Conflicts of interest

None.

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