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SHORT COMMUNICATION

Dezocine pretreatment prevents myoclonus induced by etomidate: a randomized, double-blinded controlled trial

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Abstract The aim of this randomized, double-blind, placebo-controlled clinical trial was to evaluate the effects of dezocine on the incidence and severity of myoclonus induced by etomidate. Patients (108) were randomly assigned to one of two groups to receive either 0.1 mg kg^{-1} of dezocine ($n = 54$; Group D) or saline ($n = 54$; Group S) intravenously 1 min before 0.3 mg kg^{-1} etomidate was given. The occurrence and severity (observational score of 0–3) of myoclonus was assessed for 2 min after administration of etomidate. The incidence and the intensity of myoclonus were significantly lower in Group D (0 %) than in Group S (75.9 %) ($P < 0.01$), and all patients showed stable cardiovascular profiles. The results suggest that infusion of 0.1 mg kg^{-1} dezocine 1 min before etomidate administration is effective for suppressing myoclonus induced by etomidate during induction of general anesthesia without significant side-effects.

Keywords Anesthetics · Etomidate · Dezocine · Complications · Myoclonus

Etomidate is advocated as an agent for induction of anesthesia for hemodynamically compromised patients because it produces few cardiopulmonary side-effects and has a stable cardiovascular profile. However, this drug is associated with two disturbing side-effects—pain on injection and myoclonus. Pain on injection has been ameliorated by use of a lipid formulation of etomidate (Etomidate-Lipuro) [1], but myoclonic movements still develop in 50–80 % of non-premedicated patients [2]. Myoclonic movements may lead to patient discomfort and present a problem to those who have only partial cardiovascular reserves. Myoclonus may also be detrimental to patients with open globe injuries and in emergency non-fasting conditions [3]. In patients with epilepsy, myoclonus can enhance focal epileptogenic activity [4, 5].

The myoclonus after etomidate administration may represent a type of seizure [6–8]. Agonistic modulation of κ opiate receptors limits seizures [9, 10] and dezocine acts mainly in this manner. Since the effectiveness of pretreatment with dezocine on myoclonic activity has not been previously investigated, the aim of the present study was to evaluate dezocine pretreatment on the incidence and severity of myoclonus during induction of anesthesia with etomidate.

Ethical approval for this study was provided by the Institutional Ethics Committee of the 2nd Affiliated Hospital of Nanjing Medical University, and this study was registered in the Chinese Clinical Trial Registry (ID: ChiCTR-PRC-13003152). All patients involved have given their written, informed consent.

Trial registration: Chinese Clinical Trial Registry (ID: ChiCTR-PRC-13003152). The registration information can be found on the following website: http://apps.who.int/trialsearch/Trial.aspx?TrialID=ChiCTR-PRC-13003152.

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Patients with neurological diseases, drug allergies, and those who had received analgesics, sedatives, or opioids within the previous 24 h were excluded. One hundred and eight patients with American Society of Anesthesiologists (ASA) physical status I or II, aged 20–65 years, and undergoing general anesthesia for elective surgical procedures were enrolled.

Patients were randomly assigned to one of two groups to receive either dezocine (0.1 mg kg^{-1}; $n = 54$; Group D) or saline ($n = 54$; Group S). Randomization was achieved by use of a computer-generated table of random numbers. Drugs were prepared in black 10-ml syringes outside the operating room by an anesthesiologist who was not involved in the induction of anesthesia.

At 30 min before patients arrived at the operating room, 0.5 mg of atropine was injected intramuscularly to decrease upper airway secretions. Before anesthesia, standard monitors, including those for electrocardiography, noninvasive blood pressure measurement, and pulse oximetry (SpO_2) were applied, and 0.9 % saline was infused at 300 ml h^{-1}.

After oxygenation for 2 min, the pretreatment drug was infused over 30 s. At 1 min after infusion, anesthesia was induced with the lipid formulation of etomidate (Etomidate-Lipuro, 0.3 mg kg^{-1}) over a period of 30 s. At 2 min after administration of etomidate and evaluation of myoclonus, vecuronium (0.1 mg kg^{-1}) and fentanyl (3 μg kg^{-1}) were given to facilitate tracheal intubation.

Patients were observed continuously for myoclonus by a physician who was blinded to the pretreatment drug. The patients also were not aware of the pretreatment drug. Myoclonic movements were defined as involuntary short contractions of muscles leading to a short, observable movement of body parts. The intensity of myoclonus was graded as 0, no myoclonus; 1, mild myoclonus (short movements of a body segment, e.g., a finger or wrist only); 2, moderate myoclonus (mild movements of two different muscles, e.g., face and leg); or 3, severe myoclonus (intensive clonic movements in two or more muscle groups, e.g., fast adduction of a limb) [2].

By asking the patient about any discomfort after infusing the dezocine and before the induction of anesthesia with etomidate, side-effects including headache, dizziness, and nausea were checked by another anesthesiologist who was blinded to the groups in order to avoid bias of the investigators who had observed myoclonus. Heart rate, noninvasive arterial blood pressure, and oxygen saturation were recorded every minute during the study period.

Based on results of a preliminary study, we expected the frequency of myoclonus in Group S to be approximately 0.7. Power analysis showed that a sample size of 54 patients per group had a 90 % power to detect a reduction rate of 0.3, with $\alpha = 0.05$ (1-tailed), and 15 % dropout.

Table 1 Frequency and severity of myoclonic movement after etomidate injection ($n = 54$, chi-squared test)

	No myoclonus	Myoclonus			Frequency (%)
		Mild	Moderate	Severe	
Group D	54*	0*	0*	0*	0*
Group S	13	7	10	24	75.9

* $P < 0.01$ vs group S

Table 2 Number of side-effects

	Group D ($n = 54$)	Group S ($n = 54$)
Headache	0	0
Dizziness	3	0
Nausea	1	0

Data were presented as numbers of patients for categorical variables and mean ± SD deviation for normally distributed data. Statistical analyses were performed with Graphpad Prism 5.0 (San Diego). Non-parametric statistical procedures were used in all analyses. Demographic data were analyzed with Mann–Whitney's test for comparison of two means. A P value < 0.05 was considered to be significant.

In total, 108 patients were assessed for eligibility. No case was excluded from the trial, and all cases were analyzed. The demographic characteristics (age, gender, weight, and ASA physical status) were similar between the groups (Table 1S).

The incidence and intensity of myoclonus were significantly lower in Group D (0 %) than in Group S patients (75.9 %) ($P < 0.01$) (Table 1).

The side-effects in the two groups were similar with regard to headache, dizziness, and nausea (Table 2). The saturation of peripheral oxygen (SpO_2) was >97 % in all subjects. All patients showed stable cardiovascular profiles. In no case, was there a problem with bradycardia or hypotension during the study period.

The present data show that pretreatment with 0.1 mg kg^{-1} dezocine completely inhibits the incidence and severity of myoclonic movements during induction of anesthesia with etomidate.

A variety of agents have reduced myoclonus to different extents, the most effective way being by pretreatment with opioids. Higher doses of opioids effectively reduce myoclonic movements, but at the cost of undesirable side-effects, such as apnea and chest wall rigidity. Pretreatment with 100, 250, 500 μg of fentanyl administered intravenously 5 min prior to etomidate-induced anesthesia reduced the incidence of myoclonus to 33, 13, and 0 %, respectively but increased the incidence of apnea by 87, 87,

and 100 %, respectively [11]. In a study by Hueter et al. [12], no female patients pre-treated with 0.3 μg kg^{-1} sufentanil experienced myoclonus, while 80 % of the patients in the placebo group developed myoclonic movements. In their study, midazolam 7.5 mg was administered orally 1 h prior to induction of anesthesia. Because midazolam can also reduce etomidate-induced myoclonic movements [13], the results may be due to the effect of the combination of both agents. Furthermore, >60 % of patients treated with sufentanil showed mild to severe sedation, and 6 of 20 patients had a respiratory rate <10. The effect of plasma concentrations of remifentanil of 0, 2, or 4 ng ml^{-1}, controlled by an infusion system, showed incidence rates of 81, 12, and 0 %, respectively [14]. However, in the group pretreated with 4 ng ml^{-1} remifentanil, 40 % of patients developed coughs, 45 % developed chest wall rigidity, 6 % developed apnea, and 6 % showed sedation.

In the present investigation, pretreatment with 0.1 mg kg^{-1} dezocine reduced the incidence of myoclonus from 75.9 % in the placebo group to 0 %. The above side-effects were not seen, except for a few patients in group D who complained about dizziness or nausea after administration of dezocine.

Etomidate is a ligand of γ-aminobutyric acid (GABA) receptors, which suppress the reticular activating system of the central nervous system. Although many drugs have been tested to decrease the incidence of myoclonic activity after etomidate administration, the neurologic mechanism of etomidate-induced myoclonus is unclear. Some studies suggested that the myoclonic activity induced by etomidate may be associated with seizures [6–8]. The activation of κ opiate receptor can inhibit seizure activity [10, 15]. Dezocine mainly binds to and modulates κ opiate receptors, so it is likely that the mechanism of dezocine to reduce etomidate-induced myoclonus may lie in its activation through κ opiate receptor modulation as an agonist. However, the molecular mechanisms underlying the effects of dezocine on the reduction of myoclonic movements deserves further study.

There are some limitations for this clinical trial. First, the main outcome measure (rating of myoclonus) was subjective, but we did not find other accurate and convenient monitoring indicators in previous clinical studies. Secondly, we did not investigate after the optimal clinical dose of dezocine on etomidate-induced myoclonus, since there are few previously reported studies on the relationship between dezocine and myoclonus. Whether lower doses of dezocine exert the same effect without adverse side-effects will be tested in future studies.

In conclusion, intravenous infusion of 0.1 mg kg^{-1} dezocine 1 min before etomidate administration is effective in suppressing etomidate-induced myoclonic movements during induction of general anesthesia.

Conflict of interest None of the authors has any conflict of interest.

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