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SHORT COMMUNICATION

Intravenous dezocine pretreatment reduces the incidence and intensity of myoclonus induced by etomidate

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Abstract To evaluate the suppressive effect of intravenous dezocine on the incidence and severity of myoclonic movements induced by etomidate, a total of 80 patients, American Society of Anesthesiologists physical status I–II, were randomized into two equally sized groups ($n = 40$). These two groups were assigned to give either intravenous dezocine 0.1 mg/kg or a matching placebo (equal volume of 0.9 % saline) 30 s before administration of etomidate. For anesthesia induction, 0.3 mg/kg etomidate was injected over a period of 1 min. One minute after etomidate administration, the severity of myoclonus was assessed. Pretreatment with dezocine significantly reduced both the incidence and intensity of myoclonus. These results demonstrate that intravenous dezocine 0.1 mg/kg 30 s prior to induction was effective in suppressing myoclonic movements in our patients.

Keywords Etomidate · Dezocine · Myoclonus

Etomidate is a unique drug used for induction of general anesthesia and sedation. Initially developed as anti-fungal agents, the potent hypnotic activity of several compounds was observed during animal testing, and several compounds, including etomidate, appeared to be significantly safer than barbiturates. Etomidate was introduced into clinical practice as an intravenous induction agent in 1972. It has a stable cardiovascular profile and minimal respiratory side effects. Therefore, etomidate is the ideal induction agent for patients with cardiovascular compromise [1, 2]. But two disturbing side effects have been discussed in the literatures for many years; pain on injection has been solved by a new fat formulation for etomidate. But the problem of etomidate-induced myoclonus has not been solved [3]. Myoclonus is a common problem during induction of anesthesia with etomidate; 50–80 % of non-premedicated patients develop myoclonic movements [4], which may lead to patient discomfort. Myoclonus resulting from induction of anesthesia with etomidate might also be a problem in the non-fasting patient. In patients with an open-globe injury, myoclonus after etomidate raises the risk of prolapse of vitreous material as a result of high intraocular pressure [5]. In addition to myoclonus, hypertension and tachycardia are frequent after intubation as well as. The most effective way to decrease myoclonic movements is pretreatment with opioids. Fentanyl and alfentanil have been shown to be effective, but with these drugs patients still experienced myoclonus at a rate of 8–50 % [5]. Sufentanil 0.3 μg/kg given with sufficient time before etomidate reduces myoclonic muscle movements during induction of anesthesia, but with these drugs patients had a higher degree of sedation and a lower respiratory rate [6]. Pretreatment with etomidate (0.03 mg/kg), given 60 s before induction of anesthesia, is effective at reducing etomidate-induced myoclonus, without related side effects [7]. Dezocine is a synthetic opioid with partial agonist characteristics [8]. Though initially identified as a k-receptor agonist, a later study suggests that dezocine is a k-receptor antagonist [9]. In therapeutic doses dezocine does not produce clinically significant respiratory depression. Clinically important haemodynamic changes have not

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been observed with usual analgesic doses of dezocine [10]. However, no published data are yet available about the effects of dezocine on myoclonus after injection of etomidate. Therefore, we designed a placebo-controlled study of the effects of pretreatment with dezocine on the incidence and severity of myoclonus during anesthesia induction with etomidate.

This study was approved by the Ethical Committee of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, Henan, China (Registration number: ChiCTR-TRC-13004080). Before participating, patients gave their written informed consent. American Society of Anesthesiologists physical status I–II patients scheduled for elective surgery under general anesthesia were enrolled in this study.

All of the patients fasted from midnight, and were not premedicated in order to avoid pharmacodynamic and pharmacokinetic drug interactions. Patients with adrenal cortex dysfunction [11], neurologic disease, psychiatric disorders, drug allergy, or who had received sedatives, analgesics, or opioids within the previous 24 h were excluded from the study. Patients were randomly assigned at a 1:1 ratio to either dezocine ($n = 40$; Group D) administered as a 0.1 mg/kg intravenous bolus, or saline ($n = 40$; Group S) administered as a matching placebo (equal volume of 0.9 % saline) 30 s before the induction of anesthesia. Randomization was provided by use of shuffled, sealed, opaque, numbered envelopes.

On arrival at the operating room, standard monitoring was applied, and a 20-gauge cannula was inserted into a vein on the dorsum of the patient's nondominant hand and infusion of 0.9 % saline at 1. 5 ml/kg/h was started.

After preoxygenation, both agents were given intravenously over 5 min just before anesthesia induction. For anesthesia induction, 0.3 mg/kg etomidate was injected over a period of 1 min. Patients were observed continuously for myoclonus by a physician who was blinded to treatment group. SBP, DBP, heart rate (HR), and SpO2 were recorded before the administration of dezocine or normal saline (T0) and 5 min later (T1) after dezocine or normal saline injection. Assisted mask ventilation with oxygen was applied if desaturation was observed (SpO2 < 89 %). Other side effects related to dezocine, such as bradycardia or hypotension, were also recorded after the injection.

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 a wrist only); 2, moderate myoclonus (mild movements of two different muscles, e.g. face and leg); or 3, severe myoclonus (intense clonic movements in two or more muscle groups, fast adduction of a limb) [4, 12]. One minute after administration of the induction agent and evaluation of myoclonus, vecuronium 0.1 mg/kg was given to facilitate tracheal intubation. After intubation, anesthesia was maintained with sevoflurane or isoflurane in oxygen.

Table 1 characteristics of the patients receiving dezocine or saline

Variables	Group dezocine ($n = 40$)	Group saline ($n = 40$)
Age (years)	37. 2 ± 11. 7	40.5 ± 10.3
Sex (M/F)	6/34	3/37
Height (cm)	161. 8 ± 5. 1	162. 5 ± 6. 8
Weight (kg)	59. 9 ± 10.9	61. 4 ± 9. 1
ASA physical status I/II (n)	22/18	23/17

Values are expressed as mean ± standard deviation, with ASA physical status only as a number

Table 2 The incidence and severity of myoclonus in two groups

Group	Grade 0	Grade 1	Grade 2	Grade 3	Total myoclonus
Dezocine	28*	5	5	2*	12
Saline	14	3	7	16	26

* $P < 0.01$, compared to group saline

Statistical analyses were performed with SPSS18. 0 Data are presented as number of patients for categorical variables or mean ± standard deviation. Demographic data were analyzed using Student's test. Fisher's exact test was used to compare categories. The χ^2-test and analyses of variance were used to identify statistical significance. All differences were considered significant at $P < 0.05$. There were no significant differences between the two treatment groups in the patients' demographic data (Table 1). Pretreatment with dezocine significantly reduced both the incidence and severity of myoclonic movements after induction with etomidate (Table 2). Dezocine showed some degree of sedation. The SpO2 was higher than 90 % in all study patients. The hemodynamic data (SBP, DBP, HR) were also similar and there was no significant difference between the study groups (Table 3). In no case, however, was there a problem with bradycardia or hypotension.

The main finding of the present study was that dezocine 0.1 mg/kg reduces the incidence of myoclonus during anesthesia induction with etomidate. The neurologic mechanism of myoclonus is unclear, although it may be a form of seizure activity. Researchers have suggested that it is a disinhibition phenomenon, because large doses of etomidate depress cortical activity before they depress subcortical activity [13]. Doenicke et al. [4] observed that

Table 3 The incidence and severity of myoclonus in two groups

Group	HR (bpm)		SBP (mmHg)		DBP (mmHg)	
	T0	T1	T0	T1	T0	T1
Dezocine	73 ± 11	72 ± 10	121 ± 12	118 ± 10	69 ± 10	69 ± 11
Saline	76 ± 11	74 ± 8	120 ± 11	122 ± 13	72 ± 10	71 ± 10

SBP Systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *T*0 time before administration of dezocine or normal saline injection, *T*1 5 min after dezocine injection

No statistical difference was observed between the dezocine and saline group

myoclonus after etomidate is a phenomenon of subcortical disinhibition like the phenomenon of restless legs during normal human sleep and is not generated by an epileptic focus. Various methods have been used for attenuating myoclonus during IV injection of etomidate. Pretreatment with benzodiazepines and opioids, drugs known to inhibit subcortical neuronal activity, abolish myoclonus. Choi et al. [14], showed that pretreatment with rocuronium significantly reduced the frequency of myoclonus due to etomidate by blocking transmission at the neuromuscular junction. In recent research butorphanol pretreatment was the most effective in attenuating the incidence and severity of myoclonus associated with IV injection of etomidate [15]. B Un et al. [16], also reported that low-dose magnesium pretreatment before etomidate induction of anesthesia significantly reduces unwanted myoclonic jerks and also protects the haemodynamic stability. Pretreatment with dexmedetomidine or thiopental is effective in reducing the incidence and severity of etomidate-induced myoclonic muscle movements [17]. But clinically distressing side effects are frequently observed, for example, sedation, apnea, chest muscle rigidity, pain, cardiovascular depression for opioids, delayed recovery for benzodiazepines, and airway obstruction, regurgitation, and aspiration for muscle relaxants [12, 14, 17, 18].

In recent research R Liu et al. [19], revealed that the unique molecular pharmacological profile of dezocine as a partial μ-receptor agonist, a κ-receptor antagonist, and a norepinephrine and serotonin reuptake inhibitor (via norepinephrine transporter and serotonin transporter). Dezocine-induced respiratory depression reached a ceiling at a dose of approximately 0.3–0.4 mg/kg. The ceiling respiratory and analgesic activities of dezocine occurred at the same dosage, so we used dezocine 0.1 mg/kg dose for the experiment. Unlike morphine, dezocine did not cause hypotension in the group of patients [10]. This is the same as the results of our clinical trials. The site of action of dezocine in reducing the myoclonus of etomidate injection is not clear. We speculate that the analgesic action and the sedative effect of dezocine may contribute to reducing of myoclonus after etomidate administration and a norepinephrine and serotonin reuptake inhibitor. Further work is suggested for confirming the mechanism of action of in preventing etomidate-induced myoclonus.

In conclusion, we showed that IV dezocine 0.1 mg/kg given 30 s before etomidate administration reduces myoclonic muscle movements during induction of anesthesia, without significant side effects.

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