Prevention of etomidate-induced myoclonus during anesthetic induction by pretreatment with dexmedetomidine

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Abstract

Myoclonus induced by etomidate during induction of general anesthesia is undesirable. This study evaluated the effect of dexmedetomidine (DEX) pretreatment on the incidence and severity of etomidate-induced myoclonus. Ninety patients undergoing elective surgical procedures were randomly allocated to three groups (n = 30 each) for intravenous administration of 10 mL isotonic saline (group I), 0.5 µg/kg DEX in 10 mL isotonic saline (group II), or 1.0 µg/kg DEX in 10 mL isotonic saline (group III) over 10 min. All groups subsequently received 0.3 mg/kg etomidate by intravenous push injection. The incidence and severity of myoclonus were recorded for 1 min after etomidate administration and the incidence of cardiovascular adverse events that occurred between the administration of the DEX infusion and 1 min after tracheal intubation was recorded. The incidence of myoclonus was significantly reduced in groups II and III (30.0 and 36.7%), compared with group I (63.3%). The incidence of severe sinus bradycardia was significantly increased in group III compared with group I (P<0.05), but there was no significant difference in heart rate in groups I and II. There were no significant differences in the incidence of low blood pressure among the 3 groups. Pretreatment with 0.5 and 1.0 µg/kg DEX significantly reduced the incidence of etomidate-induced myoclonus during anesthetic induction; however, 0.5 µg/kg DEX is recommended because it had fewer side effects.

Key words: Dexmedetomidine; Etomidate; Myoclonus

Introduction

When introduced in 1973, etomidate was a novel induction agent with a stable cardiovascular profile and minimal respiratory side effects, and as such is still widely used for hemodynamically unstable patients (1). However, it has two well-known and disturbing side effects, injection pain and myoclonus, that have been widely discussed in the literature. Injection pain has been minimized by a new lipid formulation of etomidate (2). However, suppression of myoclonus continues to be a clinical problem as a common side effect of etomidate administration during induction of anesthesia. The incidence of myoclonus has been reported to be as high as 50-80% (3). The consequences of this side effect can be serious in nonfasted emergency patients, patients with open eye injuries, or patients with limited cardiovascular reserves (4).

Although the mechanism of etomidate-induced myoclonus is still not clear, a number of drugs have been investigated for their ability to suppress these myoclonic movements. Pretreatment with benzodiazepines (5), opioids (6), and rocuronium (7) have been shown to reduce myoclonus to some extent. Dexmedetomidine (DEX) is a strong, highly selective α2-adrenoceptor agonist with a wide spectrum of pharmacological properties. It provides sedation, anxiolysis, and hypnosis, as well as analgesia, and has sympatholytic properties. However, few studies have evaluated the effects of DEX on myoclonus after etomidate injection. This study aimed to investigate the effects of DEX pretreatment on the incidence and severity of myoclonus during anesthesia induction with etomidate.

Patients and Methods

Patient population

This study was approved by the First People's Hospital of Lianyungang, China; eligible participants gave written informed consent. The study population consisted of 90 patients of both genders, aged 18 to 60 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective surgery under general anesthesia. Inclusion criteria were a body mass index ≤35 kg/m², no bradycardia, no upper respiratory infection during the 2 weeks before surgery, no history

of asthma, no chronic cough, and no routine use of angiotensin-converting enzyme inhibitors. Patients with adrenal cortex dysfunction, neurologic disease, psychiatric disorders or drug allergy, or who had received sedatives, analgesics, or opioids within the previous 24 h were excluded.

Patients were randomly allocated to 3 groups of 30 patients each using a computer-generated table of random numbers, and given isotonic saline (group I), 0.5 µg/kg DEX (group II), or 1.0 µg/kg DEX (group III).

Anesthesia induction and data collection

None of the patients received any premedication. After entering the operating room, all patients were given an electrocardiogram (ECG), and their pulse oxygen saturation (SpO_2), blood pressure (BP), heart rate (HR), and bispectral index (BIS) were monitored. A 20-gauge cannula was inserted into the dorsum of the patient's hand and connected to a T-connector for drug administration; Ringer lactate was infused at a rate of 4-6 mL/min. Before anesthesia induction, 0.5 or 1.0 µg/kg dexmedetomidine (batch #13070534; Hengrui Medicine, China) in 10 mL isotonic saline was infused in groups II or III, respectively, over 10 min. In group I, 10 mL isotonic saline was infused over 10 min. When the infusion was completed, 0.3 mg/kg etomidate (batch #20131106; Enhua Medicine, China) was injected intravenously over a period of 1 min.

Patients were observed continuously for myoclonus for 1 min by a physician who was blinded to all group treatments. Myoclonic movements were defined as involuntary short muscle contractions leading to short observable movements in parts of the body. 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); and 3, severe myoclonus (intense clonic movements in two or more muscle groups, e.g., fast adduction of a limb).

After administration of etomidate and evaluation of myoclonus, all patients were injected with 3 µg/kg fentanyl. When the BIS index was less than 50, 0.15 mg/kg cisatracurium was given to facilitate tracheal intubation. Maintenance anesthesia was provided by sevoflurane with 50% oxygen and 50% air to achieve a BIS value of 45-55 and a 1 µg/kg remifentanil bolus followed by 0.5 µg·kg^{-1}·min^{-1}. Mechanical ventilation was administered to maintain an end-expiratory carbon dioxide concentration of 35-40 mmHg.

Between DEX infusion and 1 min after tracheal intubation, an intravenous injection of 50 µg phenylephrine was administered if blood pressure was low (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg), or an intravenous injection of 0.5 mg atropine was administered if severe sinus bradycardia (HR <50 bpm) occurred. Occurrences of low blood pressure and severe sinus bradycardia were recorded.

Statistical analyses

The incidence of myoclonus in the isotonic saline group (group I) was expected to be 80% based on previous studies (8). A minimum of 28 patients in each group was required to detect a 50% difference in the incidence of myoclonus at a significance level of 95% and a power of 80%. We included 30 patients in each group.

Data are reported as means ± SD or number and percent. Statistical analyses were performed using the Statistical Product for Social Sciences (SPSS) software 16.0 (Chicago, SPSS Inc.). The frequencies of myoclonus, low blood pressure, severe sinus bradycardia, and proportions of gender as well as ASA (American Society of Anesthesiologists) class were compared using the chi-square test or Fisher's exact test with Bonferroni correction. One-way analysis of variance (ANOVA) was used to compare the ages and weights among the 3 groups. $P < 0.05$ was considered to be statistically significant.

Results

Demographic characteristics

There were no significant differences among the 3 groups with regard to age, gender, weight, or ASA class (Table 1).

Incidence and severity of etomidate-induced myoclonus

The incidence of myoclonus after etomidate injection was 63.3% in group I, 36.7% in group II, and 30.0% in group III. Both groups II and III had a significantly lower incidence of myoclonus than group I ($P < 0.05$), and the difference between groups II and III was not significant. There were no significant differences in the severity of myoclonus among the 3 groups (Table 2).

Incidence of low blood pressure and severe sinus bradycardia

Low blood pressure had an incidence of 6.7, 10.0, and 13.3% in groups I, II, and II, respectively, and there were

Table 1. Comparison of demographics among the 3 groups.

Demographics	Group I	Group II	Group III
Age (years)	41 ± 9	43 ± 11	40 ± 10
Gender (M/F)	16/14	13/17	15/15
Weight (kg)	63 ± 8	60 ± 7	61 ± 10
ASA (I/II)	20/10	19/11	21/9

Data are reported as means ± SD or number for n = 30 patients/group. Group I: 10 mL isotonic saline; group II: 0.5 µg/kg dexmedetomidine (DEX) in 10 mL isotonic saline; group III: 1.0 µg/kg DEX in 10 mL isotonic saline. There were no statistically significant differences among the 3 groups with regard to age, gender, weight or ASA (American Society of Anesthesiologists) class (chi-square test or one-way ANOVA).

Table 2. Comparison of incidence and severity of myoclonus among the 3 groups.

Myoclonus	Group I	Group II	Group III
Incidence, n (%)	19 (63.3%)	11 (36.7%)*	9 (30.0%)*
Intensity (n)			
Grade 0	11	19	21
Grade 1	10	9	8
Grade 2	6	2	1
Grade 3	3	0	0

Data are reported as number or number and percent for $n = 30$ patients/group. Group I: 10 mL isotonic saline; group II: 0.5 µg/kg dexmedetomidine (DEX) in 10 mL isotonic saline; group III: 1.0 µg/kg DEX in 10 mL isotonic saline. Myoclonus intensity: grade 0, no myoclonus; grade 1, mild myoclonus; grade 2, moderate myoclonus; grade 3, severe myoclonus. *$P < 0.05$, groups II and III *vs* group I (Fisher's exact test).

no significant differences among the 3 groups. Severe sinus bradycardia had an incidence of 0.0, 6.7, and 24.0% in groups I, II, and III, respectively; the incidence in group III was higher than that in group I ($P < 0.05$), and there was no significant difference between groups I and II (Table 3).

Discussion

Our study demonstrated that DEX pretreatment significantly reduced the incidence of etomidate-induced myoclonus in a dose-dependent manner but had no effect on the severity of myoclonus. Pretreatment with 1 µg/kg DEX increased the risk of severe sinus bradycardia during anesthesia induction, but intravenous injection of atropine 0.5 mg was useful for reversing that condition.

Etomidate is widely used as an anesthetic induction agent in clinical practice. Several desirable properties, such as rapid onset (9), brevity of action (10), lack of cardiovascular depression (11), and protection of intracranial pressure (12), make it an attractive agent for rapid sequence intubation. However, etomidate is also associated with two side effects, injection pain and myoclonus. Pain on injection has been largely eliminated by use of a lipid formulation of

Table 3. Comparison of incidences of low blood pressure and severe sinus bradycardia among the 3 groups.

Group	Low blood pressure	Severe sinus bradycardia
I	2 (6.7%)	0 (0.0%)
II	3 (10.0%)	2 (6.7%)
III	4 (13.3%)	8 (24.0%)*

Data are reported as number and percent for $n = 30$ patients/group. Group I: 10 mL isotonic saline; group II: 0.5 µg/kg dexmedetomidine (DEX) in 10 mL isotonic saline; group III: 1.0 µg/kg DEX in 10 mL isotonic saline. *$P < 0.05$, group III *vs* groups I and II (Fisher's exact test).

etomidate, but myoclonus remains a common problem during anesthesia induction. Etomidate-induced myoclonus can have serious consequences, such as vitreous prolapse in a patient with open eye injury (13). Moreover, ECG leads may become detached during myoclonic movements, and decreased oxygen saturation, as measured by pulse oximetry, has been reported (14).

Many mechanisms have been proposed to explain myoclonus. For example, it was reported that myoclonus resulted from temporal subcortical disinhibition similar to irritable leg syndrome, which is characterized by uncomfortable legs, irritability, inability to sleep, and numbness, but not related to epileptic activity (3,15,16). Many physical methods and drugs have been reported to prevent myoclonus associated with etomidate. Schwarzkopf et al. (17) observed decreased myoclonic incidence after intravenous administration of 0.015 mg/kg midazolam. However, intravenous midazolam injection could induce respiratory depression and sedation. Pretreatment with high doses (greater than 100 µg) of fentanyl before etomidate could effectively decrease the incidence of myoclonus, but also caused an increase in apnea incidence during anesthesia induction (18). Choi et al. (7) reported that pretreatment with rocuronium significantly reduced the frequency of myoclonus after etomidate injection by blocking transmission at the neuromuscular junction; however, it was accompanied with some disadvantages associated with muscle relaxants, such as airway obstruction, regurgitation, and aspiration. An ideal drug for preventing myoclonus should be short-acting, not produce significant depression on respiration and hemodynamics, and not prolong recovery from anesthesia.

DEX, an α2-adrenoceptor agonist having analgesic and anxiolytic activity, is widely used for anesthesia and intensive care (19-21). Salman et al. (22) reported that 0.5 µg/kg DEX could be used for pretreatment with etomidate without significant cardiovascular side effects, especially in patients with low cardiac reserve. Mizrak et al. (23) reported that 0.5 µg/kg DEX was effective in reducing the incidence and severity of etomidate-induced myoclonic muscle movements. In our study, we used two doses of DEX, 0.5 and 1.0 µg/kg, to evaluate its effect on the myoclonus induced by etomidate. Both doses of DEX significantly reduced the incidence of myoclonus from 63.3% without pretreatment to 36.7% at 0.5 µg/kg and 30.0% at 1.0 µg/kg, which is similar to the results reported by Mizrak et al. (23). At the higher dose of DEX, the incidence of hypotension and severe sinus bradycardia was increased, but there were no significant differences in low blood pressure among the 3 groups. Compared with groups I and II, the incidence of severe sinus bradycardia in group III increased significantly. Bradycardia and hypotension are the major side effects observed following DEX infusion, and bradycardia is attributed to a reflex response to transient hypertension at the beginning of infusion. Transient hypertensive responses have been observed with higher DEX doses (1-4 µg/kg). This is attributed to

initial stimulation of α-2B adrenergic receptors present in vascular smooth muscles. A subsequent decrease in heart rate is due to a decrease in central sympathetic outflow. Koroglu et al. (24) reported that a high dose of DEX (a bolus of 2-3 μg/kg over 10 min or infusion of 1.5-3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in children undergoing MRI produced bradycardia in 16% of the patients. Hypotension is attributed to decreased central sympathetic outflow. In our study, there were no significant differences in the incidence of hypotension among the 3 groups. Our findings suggested that 0.5 μg/kg DEX infusion over 10 min before anesthetic induction may be safer.

A limitation of this study was that we used only two doses of DEX to evaluate its effect on myoclonus induced by etomidate. We used only two doses because previous studies showed that DEX used as a premedicant at doses of 0.5-1 μg/kg had sedative and anesthetic-sparing effects, as well as attenuating airway/circulatory reflexes during anesthesia (25). Further studies are required to determine the minimal dose of DEX that will suppress myoclonic movements without causing side effects. Moreover, we infused DEX by an infusion pump over 10 min. Under some emergency conditions, the time should be shorter; thus it is necessary to find another way of administering DEX more rapidly and without side effects.

In conclusion, this study showed that pretreatment with DEX at 0.5 and 1.0 μg/kg before etomidate administration during anesthetic induction could significantly reduce the incidence of myoclonus. DEX at 0.5 μg/kg is recommended because it is associated with fewer side effects.

Acknowledgments

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