

Comparative study evaluating efficacy of sufentanil versus midazolam in preventing myoclonic movements following etomidate

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Abstract

Background and Aims: Myoclonus is a major side-effect following etomidate injection requiring use of medical intervention.

Material and Methods: In this double-blinded clinical trial, 50 consecutive patients, randomly received sufentanil 0.2 µg/kg or midazolam 0.015 mg/kg, 90 s before induction of anesthesia with etomidate (0.3 mg/kg). Then, the patients were monitored for any myoclonic movements during anesthesia.

Results: The incidence of myoclonus was 28% in the sufentanil group and 84% in the midazolam group. The frequency and intensity of myoclonus were significantly higher in the midazolam group, compared to the sufentanil group ($P < 0.001$). Myoclonus duration in the sufentanil and midazolam groups were 5.8 ± 13.2 and 69 ± 47.8 s, respectively ($P < 0.0010$).

Conclusion: The frequency, intensity and duration of myoclonus in the midazolam group, were significantly more prevalent than the sufentanil group.

Key words: Etomidate, midazolam, myoclonus, sufentanil

Introduction

Etomidate is a popular anesthetic agent since it is associated with hemodynamic stability,^[1] minimal respiratory depression,^[2] cerebral protection,^[3,4] and rapid recovery after either a single dose or a continuous infusion.^[5] However, this agent is associated with a frequent incidence of myoclonic movements.^[6]

The mechanism of myoclonus is not clear and does not seem to be associated with seizure-like electroencephalographic activities.^[7] However, myoclonus is believed to be the result of activities either in the brainstem or deep cerebral structures. The incidence of myoclonus is highly variable (0-80%) and

can be problematic in patients with open globe injuries or those at high risk of aspiration.^[8]

The incidence of myoclonus can be reduced after premedication with either opioid or benzodiazepine.^[9-12] Among the evaluated medications, both midazolam, and sufentanil, as pretreatment agents, have been reported to effectively reduce the myoclonus. However, a comparison between midazolam and sufentanil has not been made so far, and it is not clear which agent is a better option for reducing myoclonus after etomidate injection.

Therefore, we conducted a prospective, randomized, double-blind, clinical trial to compare the efficacy of midazolam and sufentanil in reducing the incidence and severity of myoclonus after etomidate injection in patients, undergoing elective ophthalmic surgery with general anesthesia.

Material and Methods

The current study was approved by the ethics committee of our university. All patients signed a written informed consent before participation. Fifty adult patients with American Society of Anesthesiologists class II or III, who were scheduled for elective eye surgery under general anesthesia, were selected for the study.

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The exclusion criteria were allergy to benzodiazepine or opioid, neuropsychological or neuromuscular diseases, adrenal dysfunction or epilepsy, addiction; and analgesic or sedatives administration within 24 h before the procedure.

Patients did not receive premedication and were randomly assigned to one of the two groups ($n = 25$ per group) Group M consisted of patients receiving midazolam (0.015 mg/kg) and group S consisted of patients receiving sufentanil (0.2 μ /kg). Randomization was performed using a computer-generated table. An anesthesiologist, who was blinded to the study and was not involved in anesthesia induction, prepared and coded syringes containing a total volume of 4 ml of medications. Patient monitoring included electrocardiography, pulse oximetry, noninvasive blood pressure (BP) monitoring, and capnography.

Patients received isotonic saline solution (5 mL/kg) over 10 min at room temperature and were preoxygenated with 100% oxygen; then, the medication was injected over 30 s. Ninety seconds after pretreatment with the medication, etomidate (0.3 mg/kg) was intravenously injected within 20 s. Two minutes after intravenous (IV) administration of etomidate, anesthesia was completed by atracurium (0.5 mg/kg) and fentanyl (2 μ /kg) to guarantee adequate anesthetic induction.

Patients were continuously monitored during anesthesia by one single physician, blinded to treatment procedures. Heart rate (HR), BP and mean arterial pressure (MAP) in pre- and post-induction (90 s after administration) were recorded.

The intensity of myoclonus was clinically graded as follows: 0 = no myoclonus, 1 = mild myoclonus (short movement of a body segment), 2 = moderate myoclonus (mild movements of two different muscles), and 3 = severe myoclonus (intense clonic movements in two or more muscle groups).^[10]

Statistical considerations

Based on previous studies, a minimum number of 23 patients were required in each group (with a significance level of 90% and a power of 80%).^[9,10] Hence, 25 patients in each group were included in this study. Statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, US). *T*-test and Chi-square were performed to compare patients' characteristics, and comparisons between the groups were performed by Mann-Whitney test. $P < 0.05$ was considered statistically significant.

Results

Demographic information of the patients is shown in Table 1; there was no significant difference between the two groups

in terms of age, although they were different regarding sex distribution ($P = 0.047$) [Table 1].

The incidence of myoclonus was significantly different between the two groups; it was 28% (7 patients) in the sufentanil group and 84% (21 patients) in the midazolam group ($P = 0.001$). The intensity of myoclonus was also significantly more severe in midazolam groups compare to sufentanil group [Table 2].

The mean duration of myoclonus was significantly less in sufentanil group than in midazolam group (5.8 ± 13.2 s vs. 69 ± 47.8 s; $P < 0.001$).

There was a significant difference in HR pre- and post-anesthesia induction in the sufentanil group. The mean HR was 83.96 ± 18.1 before the induction and 71.8 ± 15.2 after the induction in this group ($P < 0.001$). However, the difference in HR before and after the induction in the midazolam group was not significant (77.24 ± 15.1 vs. 76.2 ± 13) ($P = 0.705$).

Mean arterial pressure was significantly different before and after the induction in the sufentanil group; it was 120.46 ± 15.4 mmHg before the induction and 109.5 ± 18.8 mmHg after the induction ($P = 0.0001$). However, MAP was not significantly different before and after the induction in the midazolam group; it was 123.12 ± 19 mmHg before the induction and 116.2 ± 25.5 mmHg after the induction ($P = 0.098$).

The mean HR before and after the induction was significantly different between the two groups ($P = 0.002$). The mean difference in HR before and after the induction was 12.16 ± 10.3 in the sufentanil group and 1.04 ± 13.5 in the midazolam group.

The mean of MAP before and after the induction was not significantly different between the two groups ($P = 0.406$).

Table 1: Demographic characteristics of the patients

Group	Sufentanil group	Midazolam group	P
Gender (M:F)	10:15	17:8	0.047
Age (years)	61.16 \pm 11.84	61.16 \pm 15.00	1

Age is expressed as mean \pm Standard deviation

Table 2: Severity of myoclonus in sufentanil and midazolam groups

Severity of myoclonus	Number (%)		P (Chi-square test)
	Sufentanil	Midazolam	
0	18 (72)	4 (16)	0.001
1	2 (8)	0 (0)	
2	5 (20)	8 (32)	
3	0 (0)	13 (52)	

The mean difference in MAP before and after the induction was 10.09 ± 12.6 mmHg in the sufentanil group and 6.9 ± 20 mmHg in the midazolam group.

Discussion

The current study showed that pretreatment with sufentanil $0.2 \mu\text{g}/\text{kg}$ significantly prevents the occurrence and reduces the severity of myoclonus during anesthesia induction with etomidate. The mean duration of myoclonus in the sufentanil group was significantly less than that of the midazolam group.

The mean of variations in HR before and after the induction between the two groups was significantly different, but the mean of MAP before and after the induction was not significantly different between the two groups.

Application of different medications, as pretreatment agents, has been investigated for the reduction of myoclonus after etomidate injection. Benzodiazepine has been shown to reduce etomidate-associated myoclonus.^[11] However, diazepam ($0.0625\text{-}0.0125 \text{ mg}/\text{kg IV}$) or flunitrazepam ($0.01 \text{ mg}/\text{kg IV}$) failed to reduce myoclonic movements.^[12,13] On the other hand, Doenicke *et al.* reported a significant reduction in the incidence of myoclonus when $0.1 \text{ mg}/\text{kg}$ of diazepam was administered 5 min before etomidate.^[14]

Schwarzkopf *et al.* reported that the incidence of myoclonic movements was significantly lower in patients, who were pretreated with midazolam $0.015 \text{ mg}/\text{kg}$ (20%), compared to the placebo group (90%).^[9] In this study, all patients in the study groups were premeditated with oral midazolam; however, in our study, patients did not receive premedication.

In the study by Hwang *et al.*, IV administration of midazolam 2 min before etomidate injection reduced the incidence of myoclonus up to 17%.^[15] In the current study, the incidence of myoclonus in the midazolam-treated group was 84%, which was significantly higher than that observed in the study by Hwang. In the study by Hwang, etomidate was administered 2 min after midazolam ($0.05 \text{ mg}/\text{kg}$); the higher dosage and longer interval in the study by Hwang may account for the lower incidence of myoclonus, following midazolam administration in their study, compared to ours.

Several opioids with different doses have been investigated as pretreatment medications to prevent myoclonus. Pretreatment with $100 \mu\text{g}$ of fentanyl reduced the incidence of myoclonus up to 8%.^[6] Use of higher fentanyl doses ($500 \mu\text{g}$) significantly reduced myoclonic movements; however, the incidence of apnea increased during induction.^[16]

In a study by Fassoulaki *et al.*, they found no change in myoclonic occurrence when fentanyl $100 \mu\text{g}$ was administered before anesthesia induction with etomidate.^[11]

Remifentanil ($1 \mu\text{g}/\text{kg}$), administered 2 min before etomidate injection, was reported to reduce the incidence of myoclonus to 7%, without any clinically relevant side-effects.^[17] In another study, pretreatment with remifentanil (with the same dose) was associated with a 17% incidence of myoclonus, which was higher than that observed in the study by Kelsaka *et al.* (7%). Furthermore, 10% of the remifentanil-treated patients experienced clinically relevant side-effects such as chest muscle rigidity and bradycardia. Therefore, their results suggested that remifentanil may not be a good option for routine pretreatment during etomidate injection.^[15]

Other investigators have recommended sufentanil ($0.3 \mu\text{g}/\text{kg}$) as a pretreatment agent before anesthesia induction with etomidate. In fact, this medication has been shown to completely prevent myoclonus without causing any side-effects.^[10] Studies with other opioids such as alfentanil and buprenorphine have not shown higher efficiencies.^[18,19]

In our study, pretreatment with sufentanil ($0.2 \mu\text{g}/\text{kg}$) was associated with a significantly reduced incidence and severity of myoclonus; however, pretreatment with midazolam resulted in a higher incidence and severity of myoclonus (including moderate and severe grades of myoclonus). The duration of myoclonus in the sufentanil group was also less than that of the midazolam group. Due to the findings of the current study, in the sufentanil group, HR reduced after induction, but the mean difference in MAP was not clinically significant after sufentanil administration.

Limitations

The sample of our study was small so further studies are required for comparing different doses of opioids (e.g., sufentanil) and determining other adverse effects.

Conclusion

According to the results of this study, it seems using sufentanil as a pretherapeutic agent might reduce the risk of development of etomidate-induced myoclonus.

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Conference Calendar January 2016

Name of conference	Dates	Venue	Name of organising Secretary with contact details
Ramachandra Anesthesia Continuing Education RACE 2016	January 22-24 th , 2016	SRMC Auditorium Sri Ramachandra University Porur, Chennai	Prof Mahesh Vakamudi RACE Secretariat, A6 OR Complex, Dept of Anaesthesiology Critical Care & Pain Medicine, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University, Porur, Chennai - 600116 Phone Nos: 044-23860125 Mobile: +919042606596 Web: www.raceanes.com Email: race.srmc@gmail.com
8 th National Conference of Pediatric Anesthesia	January 28 th -30 th , 2016	Scudder Auditorium, CMC Vellore	Dr. Sajan Philip George Organising Chairman Dr. Ekta Rai Organising secretary Professor Dept. of Anaesthesia Christian Medical College Vellore - 632 004 Tamilnadu, India. Ph: 0416-2282105, 2283556 Email: iapa8@cmcvellore.ac.in
31 st Annual National Conference of Indian Society for Study of Pain ISSPCON-2016	February 5 th -7 th , 2016	Indore	Dr. Pravesh Kanthed Telephone: 91 9301444007 Email Id: secretaryisspcon2016@gmail.com Website: http://www.isspcon2016.com/
17 th Annual Conference of Indian Society of Neuroanesthesiology and Critical Care ISNACC 2016	February 5 th -7 th , 2016	Bengaluru	Dr. Venkatesh H K Telephone: 919739974930 Email Id: isnacc2016@gmail.com Website: http://isnacc2016.org/index.html