

# The Effect of Preinduction with Midazolam, Fentanyl, and Ketamine on Etomidate Induced Myoclonic Muscle Movements

*Belal Khteishat MD\*, Wasfi Salaytah MD\*\*, Taha Qatawneh MD\*\*, Moath Alsagheer MD\**

## ABSTRACT

**Objective:** To compare the impact of preinduction with Fentanyl, Ketamine or Midazolam on the frequency and intensity of etomidate induced myoclonic muscle movements.

**Methods:** One hundred five adult, American Society of Anesthesiology class I, of both genders, aged 31-49 years and assigned for elective ENT, ophthalmology and general surgery at King Hussein Medical Center, during the period from July 2009 to Feb 2010 were included in this study. Subjects who had been given analgesics or sedatives during the past 24 hours were ruled out. The study was approved by the local ethics committee of the Royal Medical Services Directorate of the Jordanian Army and written informed consent was obtained from all participants. Patients were divided into one of 3 groups according to the intravenous preinduction agent received: group F, n=36, received Fentanyl 2 mcg/kg, group M, n=34, received midazolam 0.015 mg/kg and group K, n=35, received Ketamine 0.2 mg/kg, ninety seconds before the induction of general anesthesia using intravenous etomidate 0.3 mg/kg. An Anesthesiologist recorded the etomidate induced myoclonic muscle movements frequency and intensity based on a scale from 0 to 3, where 0=none, 1= mild, 2=moderate, and 3=severe myoclonus.

**Results:** Two of the 36 subjects in the fentanyl group (5.6%) reported etomidate induced myoclonic muscle movements, while four subjects (11.8%) in the Midazolam group and 22 subjects (62.9%) in the ketamine group had such movements( $P<0.05$ ).

**Conclusion:** Intravenous Fentanyl 2 mcg/kg administration preintravenous etomidate induction of general anesthesia decreases significantly the frequency and severity of etomidate induced myoclonic muscle movements.

**Key words:** Fentanyl, Ketamine, Midazolam, Myoclonic muscle movements.

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## Introduction

Myoclonus (myoclonic muscle movements) is a sudden, involuntary jerking of a single muscle or a group of muscles. It occurs in a wide range of disorders and is sometimes provoked by sudden stimuli such as loud noise.<sup>(1)</sup> Etomidate induced

myoclonic muscle movements are a frequent side effect during induction of intravenous general anesthesia. Myoclonic muscle movements are mainly of clinical significance in non fasting subjects (myoclonus might increase the risk of regurgitation and aspiration<sup>(2)</sup>), in subjects with open globe injury (myoclonus may increase the risk of

From the Departments of:

\*Anesthesia, King Hussein Medical Center, (KHMC), Amman-Jordan

\*\*General Surgery, (KHMC)

Correspondence should be addressed to Dr. W. Salaytah, Department of General Surgery, (KHMC), E- mail:wasfiah2@yahoo.com

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vitreous prolapse due to high intraocular pressure<sup>(3)</sup>) or in those who are cardiovascular compromised.

Etomidate, a carboxylated imidazole compound, is an anesthetic induction drug with a very favorable hemodynamic character. Nevertheless, it has few undesirable side effects such as electroencephalic activation and myoclonic muscle movements.<sup>(4)</sup> Etomidate induced myoclonic muscle movements are seen in up to 90% of subjects if no supplemental opioids are administered.<sup>(5)</sup>

Despite different agents including opioids or benzodiazepines have been chosen for potentially inhibiting etomidate induced myoclonus, the mechanism by which this effect is achieved is still unclear. An ideal myoclonus preventive preinduction agent must be short acting without cardiorespiratory side effects and without prolonging recovery from anesthesia. Opioids can decrease myoclonic muscle movements.<sup>(5)</sup> Fentanyl is a phenylpiperidine opioid. The potency of preinduction with a phencyclidine derivative such as ketamine to prevent etomidate induced myoclonus has been investigated.<sup>(6)</sup> Midazolam is an imidazobenzodiazepine derivative was also evaluated for such preventive impact in other studies.<sup>(2)</sup> The problem of etomidate induced preventive myoclonus and the drug of choice have yet to be identified.

This study was conducted to compare the potency of preinduction with midazolam, ketamine or fentanyl on the frequency and intensity of etomidate induced myoclonic muscle movements.

## Methods

One hundred five adult, American Society of Anesthesiology (ASA) class I, of both genders, aged 31-49 years and assigned for elective ENT, ophthalmology and general surgery at King Hussein Medical Center (KHMC), during the period from July 2009 to Feb 2010 were included in this study. Subjects who had been given analgesics or sedatives during the past 24 hours were ruled out. The study was approved by the local ethics committee of the Royal Medical Services Directorate of the Jordanian Army and written informed consent was obtained from all participants. In the operating room, an 18 gauge intravenous cannula was inserted. Subjects were allocated into one of 3 groups according to the intravenous preinduction agent used. Fentanyl (fentanyl citrate, 0.05 mg/ml, Janssen-cilag) 2 mcg/kg (group F, n=36), Midazolam (5 mg/ml, Hikma pharmaceutical - Jordan) 0.015 mg/kg (group

M, n=34) and Ketamine (Tekam 10mg/ml, Hikma ph.- Jordan) 0.2 mg/kg (group K, n=35). Ninety seconds after administration of the investigated agent, anesthesia was induced with Intravenous (I.V.) etomidate (hypnomidate 2mg/ml-Janssen-cilag Ltd) 0.3 mg/kg. Sixty seconds after etomidate administration, Atracurium 0.5 mg/kg was given to facilitate intubation. Fentanyl 2mcg/kg was given to all patients groups after they were put to sleep. Anesthesia was maintained using halothane 0.5-1% in a mixture of 70% nitrous oxide in 30% oxygen.

Randomization was performed using a non-random fashion with sealed envelopes. Neither the anesthesiologists performing the induction nor the patients were aware of the preinduction agent groups. Heart rate, oxygen saturation and noninvasive arterial blood pressure were monitored.

An anesthesiologist blinded to group division inquired and recorded frequency of etomidate induced myoclonic muscle movements during one minute after etomidate administration and its severity on a scale from 0 to 3 where 0=no myoclonus, 1=mild myoclonus (movement at the wrist only or mild fasciculation involving the face and/or distal upper and/or lower extremities), 2=moderate myoclonus (movement involving the arm only, elbow or shoulder or marked movement of the face and /or limbs) and 3=severe myoclonus (generalized response ,movement in more than one extremity or involving limbs and trunk).<sup>(6)</sup>

## Statistics

Chi square test was used for categorical comparison. Student's t test was used for parametric comparison. If t test was  $P < 0.05$ , it was recorded as significant.

To detect a 25% reduction in myoclonus after midazolam pretreatment, 32 patients per treatment would be needed.

## Results

Patient characteristics were similar between the groups regarding gender, age, weight, ASA class and type of operation (Table I).

Preinduction with ketamine did not reduce significantly the incidence or intensity of etomidate induced myoclonus compared to fentanyl or midazolam. Preinduction with fentanyl or midazolam decreased the frequency and intensity of etomidate induced myoclonus ( $P < 0.05$ ). There were no significant differences between the fentanyl and midazolam groups regarding the frequency and

**Table I.** Patients demographics (number or mean)

	Group F	Group K	Group M
Age (yr) 31-40	16	20	18
41-49	19	15	17
Weight(kg) 70-75	15	17	16
76-80	20	18	19
Gender F	14	15	15
M	21	20	20
ASA I	35	35	35
Type of surgery			
General surgery	11	12	12
ENT surgery	12	11	12
EYE surgery	12	12	11

**Table II.** Etomidate induced myoclonus. (number %)

	Frequency		Intensity		
	None	Yes	Mild(1)	Moderate(2)	Severe(3)
Group F (n=36)	34 (94.6)	2 (5.6)	1 (50)	1 (50)	0 (0)
Group K (n=35)	13 (37.1)	22 (62.9)	12 (54.6)	5 (22.7)	5 (22.7)
Group M (n=34)	30 (88.2)	4 (11.8)	2 (50)	1 (25)	1 (25)

intensity of etomidate induced myoclonus, but there were significant differences between fentanyl and ketamine groups ( $P < 0.05$ ) and between midazolam and ketamine groups ( $P < 0.05$ ) regarding the frequency and intensity of etomidate induced myoclonic muscle movements.

94.4%, 37.1% and 88.2% did not develop etomidate induced myoclonic muscle movements in groups F, K and M respectively. Regarding mild myoclonus, it was evident in 50%, 54.6% and 50% respectively in groups F, K and M, while moderate myoclonus was observed in 50%, 22.7% and 25% in the same groups. Severe myoclonus was found to be in 0% in F group, 22.7% in K group and 25% in M group. (Table II)

## Discussion

The present data demonstrated that preinduction with I.V. fentanyl 2mcg/kg and midazolam 0.015 mg/kg decreased the frequency and severity of etomidate induced myoclonus. We found few reports about fentanyl and myoclonus in literature, therefore we chose the dose of 2mcg/kg that was effective.<sup>(7)</sup> Ketamine was used at a dose of 0.2mg/kg to prevent etomidate induced myoclonus where 64% of patients experienced myoclonic movements,<sup>(6)</sup> whereas 62.9% developed myoclonus in our study. We waited 90 seconds before etomidate administration to have enough time for the investigated agents to act. We assessed myoclonus after etomidate in order to distinguish

between various actions of the preinduction agents on myoclonus.

Different studies have demonstrated that preinduction with opioids decreased etomidate induced myoclonus.<sup>(8)</sup> Preinduction with fentanyl 2 mcg/kg decreased the frequency of myoclonus to 6.7%<sup>(7)</sup> whereas 5.6% developed myoclonus in our investigation. Benzodiazepines preinduction has also been studied to decrease etomidate associated myoclonus. Huter *et al*<sup>(2)</sup> showed that the frequency of myoclonus was significantly less in subjects preinduced with 0.015mg/kg midazolam(10%) compared with placebo (50%), whereas 11.8% treated with midazolam in our study had myoclonus. Ketamine 0.2mg/kg preinduction was shown to decrease the incidence of etomidate induced myoclonus to 64%.<sup>(6)</sup> Although various agents have been tested to reduce its frequency, the mechanism of etomidate induced myoclonus is unknown. Doenicke *et al*<sup>(9)</sup> proposed that myoclonus is due to subcortical disinhibition. Fassoulaki *et al*<sup>(10)</sup> showed no effect on the myoclonic rate when giving 100mcg fentanyl before the induction of anesthesia with etomidate. There are conflicting data regarding the effect of benzodiazepines on etomidate induced myoclonus. In a previous study with low dose midazolam in premedicated subjects, myoclonus was in the rate of 20%.<sup>(11)</sup> It is vital that the preinduction for inhibiting myoclonus does not affect recovery from anesthesia.

Etomidate induced myoclonus may be clinically

relevant. Electrocardiogram (ECG) leads could be detached during myoclonus and a reduction of oxygen saturation has been shown during myoclonic muscle movement.<sup>(12)</sup>

Although opioids have been demonstrated to decrease myoclonus,<sup>(13)</sup> their mechanism of action is still unclear. In a study by Stockham *et al*<sup>(8)</sup> using 3 different doses of fentanyl, it was demonstrated that apnea is correlated with the decrease of myoclonus. In the group receiving 500mcg fentanyl, no subject had myoclonus but they were apneic and in the group receiving 100 mcg fentanyl, the frequency of myoclonus was 33%. The mechanism of the effect of ketamine is non competitive N-methyl-D-aspartate (NMDA) receptor antagonism, which in turn can ameliorate withdrawal movements caused by different chemical mediators by blocking NMDA receptor activation in the CNS (central nervous system). However, we could find one study in the literature about preinduction with ketamine before etomidate induction.

Etomidate interacts with GABA amino butyric acid type A (GABA) receptors suppressing the central nervous reticular activating system. Another reason could be that the inhibitory circuits are depressed earlier than excitatory neuronal circuits after etomidate administration.<sup>(14)</sup> With interruption of GABA neurons pathways associated with skeletal muscle control can become more sensitive allowing spontaneous nerve transmission to occur. These can finally lead to myoclonus.<sup>(15)</sup> Etomidate induced myoclonus is not centrally mediated.<sup>(16)</sup> Probably, the different effects of benzodiazepines on the different GABA receptors may explain the mechanism by which these drugs decrease the frequency of myoclonus. Etomidate is contraindicated in porphyria and adrenal failure. Both midazolam and fentanyl have demonstrated efficacy in terms of inhibiting etomidate induced myoclonus and it is recommended that midazolam is to be given in less painful or painless operation and fentanyl is to be given if postoperative analgesia is anticipated.

## Conclusion

This clinical investigation demonstrated that fentanyl 2mcg/kg or Midazolam 0.015 mg/kg, given before etomidate induction decreases myoclonic muscle movements. Ketamine was not effective significantly in decreasing the myoclonus.

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