

Impact Of Fentanyl Alone Vs. Fentanyl And Midazolam Pre-Treatment On Preventing Etomidate-Induced Myoclonus In Cardiothoracic Patients

Dr. Naveen D¹, Dr. P. B. Jamale², Dr. Vithal k dhulked³, Dr. Naseema Kanase⁴ Dr. Rabnna I. Mulla⁵, Dr. Salman mulla⁶, Dr. Meghana⁷

¹M.B.B.S. Department of Anaesthesiology, Krishna Institute Medical Sciences, KVV, Karad, Maharashtra, India

²M.D. Professor, Anesthesiology, KVVDU Karad, Maharashtra, India

³M.D. Professor, Head of the department of Anesthesiology, KVVDU Karad, Maharashtra, India

⁴M.D. Professor, Anesthesiology, KVVDU Karad, Maharashtra, India

⁵PhD. M. Sc Statistics, Department of Community Medicine, KVVDU Karad, Maharashtra, India

⁶M.D Senior resident Department of Anaesthesiology, Krishna Institute Medical Sciences, KVV, Karad, Maharashtra, India

⁷M.B.B.S. Department of Anaesthesiology, Krishna Institute Medical Sciences, KVV, Karad, Maharashtra, India

Cite this paper as: Dr. Naveen D, Dr. P. B. Jamale, Dr. Vithal k dhulked, Dr. Naseema Kanase, Dr. Rabnna I. Mulla, Dr. Salman mulla, Dr. Meghana, (2025) Impact Of Fentanyl Alone Vs. Fentanyl And Midazolam Pre-Treatment On Preventing Etomidate-Induced Myoclonus In Cardiothoracic Patients. *Journal of Neonatal Surgery*, 14 (32s), 3806-3811.

ABSTRACT

Background: A steady cardiovascular profile and little respiratory depression are among its most noteworthy therapeutic characteristics. These characteristics make etomidate particularly helpful in the management of anesthesia in patients with hemodynamic instability, such as those with shock, hypovolemia, or significant cardiac comorbidities. Because of this, etomidate is still often utilized in both emergency and elective surgical situations, particularly where preserving circulatory stability during induction is crucial. This study aims to fill this knowledge gap by evaluating the effectiveness of these pre-treatment strategies and providing information that will guide clinical practice, improve patient outcomes, and optimize perioperative care for this high-risk patient population.

Material and Methods: This prospective, randomised, double-blind study was conducted on 90 surgical patients allocated to 45 in each group. Group A patients received intravenous (IV) fentanyl 2 µg/kg and 5 mL saline. Group B patients received IV fentanyl 2 µg/kg and midazolam 0.03 mg/kg. The study drugs were administered intravenously over 30 s. Five minutes after study drug administration; etomidate 0.3 mg kg⁻¹ was administered over 60 s. Patients were observed for 1 min for occurrence and severity of EIM.

Results: The incidence of myoclonus was markedly lower in Group B (15.6%) versus Group A (48.9%), with a significant reduction in higher severity grades. Patients experiencing myoclonus showed elevated haemodynamic responses, including increased heart rate and blood pressure, emphasizing the clinical importance of preventing myoclonus during anesthesia induction.

Conclusion: According to these findings, preparation with fentanyl-midazolam provides a more secure and safe induction method, enhancing patient outcomes in high-risk surgical situations.

Keywords: Etomidate, fentanyl, midazolam, myoclonus

1. INTRODUCTION

Etomidate is a carboxylated imidazole derivative that is used as an induction agent for intravenous anesthesia. A steady cardiovascular profile and low histamine release are only two of its many benefits. However, 50% to 80% of patients who do not undergo pre-treatment before etomidate injection may experience uncomfortable myoclonic movements as a result of its use¹⁻⁴. Because of the substantial risk of etomidate-induced myoclonus (EIM), anesthesiologists are discouraged from using this medication. Furthermore, myoclonus may raise the risk of vitreous prolapse in patients with open globe injury due to elevated intraocular pressure, as well as of regurgitation and pulmonary aspiration in non-fasting patients⁵⁻⁷. Myoclonic movements may also interfere with patient monitoring by causing electrocardiogram (ECG) lead detachment⁵. Agents, such as opioids^{3, 8, 9}, benzodiazepines^{1, 8}, magnesium¹⁰ and dexmedetomidine¹¹, have been used to decrease the incidence of EIM with variable results. Previous investigators have reported a decrease in the incidence of EIM to a level of 20%-25% with

most of these pre-treatment agents¹². It has been suggested that the administration of both fentanyl and midazolam with etomidate induction may possibly eliminate EIM¹³. Pre-treatment with a combination of midazolam and fentanyl prior to the administration of etomidate is hypothesised to be better than that with either drug used alone in reducing the incidence and severity of EIM. The aim of this prospective, randomised, double-blind study was to compare the effect of pre-treatment with a combination of midazolam and fentanyl with either drug used alone on the incidence and severity of EIM in adult patients undergoing elective surgery under general anaesthesia. like India. Its early diagnosis and timely management can APH is defined as bleeding from the genital tract after 28 weeks of gestation to delivery of the baby.^{1,2}

2. METHODS & MATERIALS

Patients and researchers were blinded to group assignments in a prospective, randomised, double-blind study. All patients were given instructions to fast overnight and were given oral alprazolam the night before surgery (0.25 mg for individuals under 50 kg or 0.5 mg for those above 50 kg). Baseline monitoring (ECG, NIBP, SpO₂, and end-tidal carbon dioxide) was set up as soon as the patient entered the operation room. A computer-generated randomisation table was used to allocate patients at random to one of two groups. Group assignments were concealed in opaque envelopes to ensure allocation concealment. The study groups were as follows: Group A: Patients received intravenous (IV) fentanyl 2 µg/kg and 5 mL saline. Group B: Patients received IV fentanyl 2 µg/kg and midazolam 0.03 mg/kg. Study drugs were prepared by an independent anesthesiologist who diluted the medications to 5 mL with normal saline to maintain blinding. Before the study medications were given, baseline readings of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and SpO₂ were taken. The study medication was injected over a 30-second period. Bradycardia, hypotension, and any other adverse effects were recorded. The Ramsay drowsiness Scale was used to measure the level of drowsiness five minutes after the medication was administered. Subsequently, etomidate 0.3 mg/kg was administered over 60 seconds. Any complaints of pain during etomidate injection were noted. The time to loss of verbal contact and loss of eyelash reflex was recorded.

Statistical analysis:

IBM Statistical Package for the Social Sciences version 22.0 statistical package (IBM SPSS Corp.; Armonk, NY, USA) was used for analysis. One-way analysis of variance with post hoc (Bonferroni) tests were applied to determine the significant mean among the three groups. Chi-square tests were applied to determine the association among these groups for demographic and clinical characteristics. Descriptive statistics were expressed as mean and standard deviations for interval variables and as frequency with percentages for categorical variables. A p-value 0.05 (two tailed) was considered as statistically significant.

3. RESULTS

A total of 90 patients were assessed for eligibility. Of the 90 patients, 45 each group were included from the study.

Table-1: Age Distribution of Patients in Group F and Group FM

Age group	Group A (n=45)	Group B (n=45)	p value
	n (%)	n (%)	
18-30	7 (15.6%)	9 (20.0%)	0.924(NS)
31-40	16 (35.6%)	14 (31.1%)	
51-60	12 (26.7%)	13 (28.9%)	
>61	10 (22.2%)	9 (20.0%)	
Mean ± SD	36.84 ± 11.90	36.72 ± 13.02	0.96(NS)

The above table 1. showed that in Group F and Group FM showed a relatively similar pattern. In Group F, the largest proportion of patients was in the 31-40 age group (35.6%), followed by the 51-60 age group (26.7%). In Group FM, the 31-40 age group also had the highest proportion (31.1%), with the 51-60 age group following closely at 28.9%. Both groups mean ages were similar, with Group F's mean age being 36.84 ± 11.90 years and Group FM's mean age being 36.72 ± 13.02 years. The difference in age distribution between Group F and Group FM is not statistically significant (p value= 0.96)

Table-2: Gender Distribution of Patients in Group F and Group FM

Gender	Group A (n=45)	Group B (n=45)	p value
	n (%)	n (%)	
Male	18 (40.0%)	15 (33.3%)	0.797(NS)
Female	27 (60.0%)	30 (66.7%)	

Table 2. showed that in Group F and Group FM showed a noticeable difference in the proportion of male and female participants. In Group F, 60% of the patients were female (27 cases), while 40% were male (18 cases). In Group FM, the proportion of females increased to 66.7% (30 cases), and the male participants made up 33.3% (15 cases). Both groups had a total of 45 participants, with the gender distribution varying slightly between the two groups.

Table-3: ASA Classification of Patients in Group F and Group FM

ASA class	Group A (n=45)	Group B (n=45)	p value
	n (%)	n (%)	
II	30 (66.67%)	29 (64.44%)	0.86(NS)
III	10 (22.22%)	12 (26.67%)	
IV	5 (11.11%)	4 (8.89%)	

The above table 3. showed that in Group F, 30 cases (66.67%) were classified as ASA II, 10 cases (22.22%) as ASA III, and 5 cases (11.11%) as ASA IV. In Group FM, 29 cases (64.44%) were ASA II, 12 cases (26.67%) were ASA III, and 4 cases (8.89%) were ASA IV. Both groups had a total of 45 cases each.

Table-4: Anthropometric Characteristics of Patients in Group F and Group FM

Parameter	Group A (n=45)	Group B (n=45)	p value
	Mean \pm SD	Mean \pm SD	
Height (cm)	1.58 \pm 0.9	1.57 \pm 0.07	0.941(NS)
Weight (kg)	59.74 \pm 12.80	58.61 \pm 11.76	0.664(NS)
BMI (kg m-2)	23.56 \pm 4.28	22.78 \pm 4.12	0.381(NS)

Table 4. showed that in Group F and Group FM were quite similar. In terms of height, the mean was 1.58 \pm 0.9 cm for Group F and 1.57 \pm 0.07 cm for Group FM. Regarding weight, Group F had a mean of 59.74 \pm 12.80 kg, while Group FM had a mean of 58.61 \pm 11.76 kg. The BMI (Body Mass Index) was also comparable, with Group F having a mean of 23.56 \pm 4.28 kg/m² and Group FM having a mean of 22.78 \pm 4.12 kg/m². The difference in anthropometric characteristics between Group F and Group FM is not statistically significant.

Table-5: LVC and LOC Times in Group F and Group FM

Parameter	Group A (n=45)	Group B (n=45)	p value
	Mean \pm SD	Mean \pm SD	
LVC time (s)	44.76 \pm 10.12	39.55 \pm 9.96	0.0158(S)
LOC time (s)	54.12 \pm 10.2	45.74 \pm 10.32	0.0002(S)

The mean LVC (Loss of Verbal Contact) time and LOC (Loss of Consciousness) time were measured in both Group F and Group FM. Group F had a mean LVC time of 44.76 \pm 10.12 seconds, whereas Group FM had a slightly shorter mean LVC time of 39.55 \pm 9.96 seconds. For LOC time, Group F had a mean of 54.12 \pm 10.2 seconds, while Group FM had a shorter mean of 45.74 \pm 10.32 seconds. The findings indicate that, in comparison to Group F, Group FM had a faster onset of both

LVC and LOC. The difference in LVC and LOC Times in between Group F and Group FM is statistically significant.

Table-6: Incidence and Onset Time of Myoclonus in Group F and Group FM

Parameter	Group A (n=45)	Group B (n=45)	p value
Incidence	22 (48.9%)	7 (15.6%)	0.0016(S)
Onset time (s) (Mean \pm SD)	100.12 \pm 39.28	103.83 \pm 31.62	0.623(NS)

With 48.9% (22 cases) of myoclonus occurring in Group F and only 15.6% (7 cases) in Group FM, the incidence of myoclonus was substantially greater in Group F than in Group FM. Regarding the onset time of myoclonus, Group F had a mean onset time of 100.12 \pm 39.28 seconds, while Group FM had a slightly longer mean onset time of 103.83 \pm 31.62 seconds. This data suggests a lower incidence of myoclonus and a slightly delayed onset in Group FM compared to Group F. The difference in incidence in between Group F and Group FM is statistically significant. Whereas onset is not statistically significant.

Table-7: Severity Grade of Myoclonus in Group F and Group FM

Severity grade	Group A (n=45)	Group B (n=45)	p value
	n (%)	n (%)	
Grade 0	23 (51.1%)	38 (84.4%)	0.007(S)
Grade 1	7 (15.6%)	3 (6.7%)	
Grade 2	5 (11.1%)	2 (4.4%)	
Grade 3	10 (22.2%)	2 (4.4%)	

The severity of myoclonus was significantly lower in Group FM compared to Group F. In Group F, the majority of cases (51.1%) were graded as Grade 0, indicating no myoclonus, while 22.2% of cases were classified as Grade 3, the most severe level. In Group FM, 84.4% of patients had Grade 0 myoclonus, and only a small percentage (4.4%) experienced Grade 3 or Grade 2 myoclonus. Additionally, Grade 1 myoclonus was observed in 15.6% of Group F patients, compared to just 6.7% in Group FM. With 48.9% (22 cases) of myoclonus occurring in Group F and only 15.6% (7 cases) in Group FM, the incidence of myoclonus was substantially greater in Group F than in Group FM. The p-value for the severity grade distribution of myoclonus between Group F and Group FM is 0.0077. This indicates a statistically significant difference between the two groups.

Table-8: Haemodynamic Changes in Patients, with and without Myoclonus

Parameter	Myoclonus Present	Myoclonus Absent	p-value
	(Mean \pm SD)	(Mean \pm SD)	
Heart Rate(bpm)	84.45 \pm 14.	48 77.48 \pm 10.59	0.0107(S)
SBP (mmHg)	125.64 \pm 18.64	117.00 \pm 13.92	0.0146(S)
DBP (mmHg)	84.89 \pm 15.72	78.31 \pm 13.76	0.0374(S)
MAP (mmHg)	98.77 \pm 17.78	91.05 \pm 12.65	0.0198(S)

In cardiothoracic patients undergoing etomidate induction, those who developed myoclonus exhibited higher haemodynamic parameters compared to those without myoclonus. The mean heart rate was 84.45 \pm 14.48 bpm in patients with myoclonus versus 77.48 \pm 10.59 bpm in those without. Similarly, systolic blood pressure (SBP) was elevated at 125.64 \pm 18.64 mmHg compared to 117.00 \pm 13.92 mmHg, diastolic blood pressure (DBP) at 84.89 \pm 15.72 mmHg versus 78.31 \pm 13.76 mmHg, and mean arterial pressure (MAP) at 98.77 \pm 17.78 mmHg compared to 91.05 \pm 12.65 mmHg in patients without myoclonus. These findings showed a notable increase in haemodynamic responses in the presence of etomidate-induced myoclonus. The difference in hemodynamic parameters in between Group F and Group FM is statistically significant.

Discussion:

In order to optimise anaesthetic induction protocols in high-risk surgical settings, this study compares the efficacy of pre-

treatment with fentanyl alone versus a combination of fentanyl and midazolam in preventing etomidate-induced myoclonus in cardiothoracic patients. The current study's results showed that Group A and Group B patients age distributions were similar. The mean age in Group A was 36.84 ± 11.90 years, while in Group B it was 36.72 ± 13.02 years, indicating a comparable age distribution between the two groups. The findings of the present study are supported by previous literature. Adinehmehr L et al¹⁴. (2019) reported that the mean age of their studied population was 69.68 ± 12.0 years. Similarly, Isitemiz I et al¹⁵. (2014) found that the mean age of participants across groups was comparable, with Group F having a slightly higher mean age of 46 ± 12 years, while Group FM had a mean age of 44 ± 15 years. Prakash S. et al¹⁶. (2021) also observed comparable mean ages among groups, with Group F at 37.04 ± 12.40 years, Group M at 38.44 ± 10.86 years, and Group FM at 36.81 ± 13.04 years; the difference in age distribution was not statistically significant ($p = 0.69$). In the present study, females predominated in both groups. The both groups showed a higher proportion of female participants compared to males. The findings of the present study are supported by previous research. Similarly, Adinehmehr L et al¹⁴. (2019) reported a balanced gender distribution with 57 males and 48 females in their study population. Souvatzis X et al¹⁷. (2015) found that among their 51 patients, 35 were male and 16 were female, indicating a male predominance.

66.67% of the patients in Group A and 64.44% of the patients in Group B in the current study were classified as ASA Class II. Overall, the ASA classification distribution was comparable between the two groups. Study by Luan HF et al¹⁸. (2014), most patients also fell into ASA Class I/II across all groups. Group I consisted of 20 patients in ASA Class I and 10 in Class II. Group II had 19 patients in Class I and 11 in Class II, while Group III included 21 patients in Class I and 9 in Class II. The anthropometric traits of the patients in Group A and Group B were found to be similar in the current investigation. Luan HF et al¹⁸. (2014) reported that the mean body weight was comparable across the study groups, with Group I exhibiting an average weight of 63 ± 8 kg, Group II at 60 ± 7 kg, and Group III at 61 ± 10 kg. Similarly, ISitemiz I et al¹⁵. (2014) observed slight variations in body weight among the groups. Group NP had the highest mean weight (78.8 ± 13.1 kg), followed by Group FM (74.1 ± 12.8 kg), Group F (72.2 ± 15.9 kg), and Group M with the lowest (68.1 ± 15.4 kg). In terms of height, measurements were relatively similar.

The mean LVC (laryngeal vestibule closure) and LOC (laryngeal opening closure) times were shorter in Group B compared to Group A. Prakash S et al¹⁶. (2021) found statistically significant differences in LVC time, with Group FM having a shorter time (40.59 ± 9.97 seconds) compared to Group F (45.01 ± 10.32 seconds) and Group M (46.54 ± 9.16 seconds) ($p=0.001$). Similarly, the LOC time was significantly shorter in Group FM (46.93 ± 10.27 seconds) than in Group F (54.43 ± 10.0 seconds) and Group M (55.83 ± 9.33 seconds) ($p=0.001$). In this study the incidence of myoclonus was notably higher in Group A, occurring in 48.9% (22/45) of cases, compared to 15.6% (7/45) in Group B. The mean onset time of myoclonus was comparable between the groups, with Group A showing an onset time of 100.12 ± 39.28 seconds and Group B 103.83 ± 31.62 seconds. Similarly, ISitemiz I et al¹⁵. (2014) found that the incidence of myoclonus was 85% in Group NP, 40% in Group F, 70% in Group M, and 25% in Group FM, with Group F and Group FM showing noticeably lower rates. This study demonstrated that Group FM had a significantly lower severity of myoclonus compared to Group F. Similarly, Sojitra NP et al¹⁹. (2023) found that 18% of patients in Group F experienced Grade 1 myoclonus, compared to 32% in Group D. Additionally, 8% of patients in Group F exhibited Grade 2 myoclonus. In the current study, patients who exhibited myoclonus showed significantly higher haemodynamic parameters compared to those without myoclonus. Furthermore, patients who developed myoclonus showed higher haemodynamic parameters (heart rate, SBP, DBP, MAP) than those without myoclonus, indicating greater physiological stress. All things considered, these results imply that fentanyl-midazolam premedication reduces etomidate-related myoclonic activity and the corresponding haemodynamic effect in cardiothoracic patients more effectively than fentanyl alone.

4. CONCLUSION

The current study sheds information on how well fentanyl-midazolam pretreatment works to lower the incidence and severity of etomidate-induced myoclonus in patients undergoing cardiothoracic surgery as compared to fentanyl alone. Additionally, myoclonus patients displayed heightened hemodynamic reactions, such as elevated blood pressure and heart rate, highlighting the clinical significance of avoiding myoclonus during anesthetic induction. According to these findings, preparation with fentanyl-midazolam provides a more secure and safe induction method, which enhances patient outcomes in high-risk surgical situations.

REFERENCES

- [1] Schwarzkopf KR, Hueter L, Simon M, Fritz HG. Midazolam pretreatment reduces etomidate-induced myoclonic movements. *Anaesth Intensive Care* 2003; 31: 18-20.
- [2] Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, Ostwald P. Reducing myoclonus after etomidate. *Anesthesiology* 1999; 90: 113-9.
- [3] Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F, Hilken P. Fentanyl pretreatment modifies anesthetic induction with etomidate. *Anaesth Intensive Care* 1998; 16: 171-6.
- [4] Giese JL, Stockham RJ, Stanley TH, Pace NL, Nelissen RH. Etomidate versus thiopental for induction of

anesthesia. *AnesthAnalg* 1985; 64: 871-6.

- [5] Van Keulen SG, Burton JH. Myoclonus associated with etomidate for ED procedural sedation and analgesia. *Am J EmergMed* 2003; 21: 556-8.
 - [6] Huter L, Schreiber T, Gugel M, Schwarzkopf K. Low-dose intravenous midazolam reduces etomidate-induced myoclonus: a prospective, randomized study in patients undergoing elective cardioversion. *Anesth Analg* 2007; 105: 1298-302.
 - [7] Berry JM, Merin RG. Etomidate myoclonus and the openglobe. *Anesth Analg* 1989; 69: 256-9.
 - [8] Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, Han SH. A comparison of midazolam with remifentanyl for the prevention of myoclonic movements following etomidate injection. *J Int MedRes* 2008; 36: 17-22.
 - [9] Khalil SN, Lawson KS, Hanis CL, Lemak NA, Ruiz RS. Alfentanil decreases myoclonus caused by etomidate. *Middle East J Anesthesiol* 1999; 15: 185-92.
 - [10] Guler A, Satilmis T, Akinci SB, Celebioglu B, Kanbak M. Magnesium sulphate pretreatment reduces myoclonus after etomidate. *Anesth Analg* 2005; 101: 705-9.
 - [11] Dey S, Kumar M. Comparison of pretreatment with dexmedetomidine with midazolam for prevention of etomidate-induced myoclonus and attenuation of stress response at intubation: A randomized controlled study. *J Anaesthesiol Clin Pharmacol* 2018; 34: 94-8.
 - [12] Do SH, Han SH, Park SH, Kim JH, Hwang JY, Son IS, Kim MS. The effect of injection rate on etomidate-induced myoclonus. *Korean J Anesthesiol* 2008; 55: 305-7.
 - [13] Hodgson RE, Burrows RC. Midazolam and etomidate for induction of anaesthesia in ophthalmic surgery. *South Afr J Anaesth Analg* 2002; 8: 4-7.
 - [14] Adinehmehr L, Shetabi H, Moradi Farsani D, Salehi A, Noorbakhsh M. Comparison of the Sedation Quality of Etomidate, Propofol, and Midazolam in Combination with Fentanyl During Phacoemulsification Cataract Surgery: A Double-Blind, Randomized, Controlled, Clinical Trial. *Anesth Pain Med*. 2019 Apr 27;9(2): e87415.
 - [15] Isitemiz I, Uzman S, Toptaş M, Vahapoglu A, Gül YG, Inal FY, Akkoc I. Prevention of etomidate-induced myoclonus: which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study. *Med Sci Monit*. 2014 Feb 16; 20:262-7.
 - [16] Prakash S, Mullick P, Virmani P, Talwar V, Singh R. Effect of Pre-Treatment with a Combination of Fentanyl and Midazolam for Prevention of Etomidate- Induced Myoclonus. *Turk J Anaesthesiol Reanim*. 2021 Feb;49(1):11-17.
 - [17] Souvatzis X, Kalogridaki M, Mavrakis HE, Kanoupakis EM, Marouli D, Vardas P, Askitopoulou H. Adding fentanyl to etomidate fails to reduce painful recall of external direct current cardioversion in adults: a randomised trial. *Hell J Cardiol*. 2015 Mar 1;56(2):142e148.
 - [18] Luan HF, Zhao ZB, Feng JY, Cui JZ, Zhang XB, Zhu P, Zhang YH. Prevention of etomidate-induced myoclonus during anesthetic induction by pretreatment with dexmedetomidine. *Brazilian Journal of Medical and Biological Research*. 2014 Oct 24; 48:186-90
 - [19] Sojitra NP, Kantharia BN, Nakum R, Padsala K. Effect of pre-treatment on induction on anaesthesia with etomidate: A comparison between dexmedetomidine and midazolam–fentanyl combination. *Current Medicine Research and Practice*. 2023 Nov 1;13(6):275-9.
-