

ORIGINAL ARTICLE

Open Access



Comparison of pretreatment with low-dose midazolam in combination with fentanyl and midazolam alone on the occurrence of etomidate-induced myoclonus—a randomized, double-blind study

Khaise Hareed, Nisha Kachru and Rupesh Yadav*

Abstract

Background: Myoclonus is reported to occur in 50–80% of patients receiving etomidate in the absence of pretreatment. The study aimed to evaluate the efficacy of pretreatment with low-dose midazolam and fentanyl, and midazolam alone to reduce the occurrence of etomidate-induced myoclonus. Sixty patients were randomly divided into 2 groups. In group MF, patients received pretreatment with intravenous (IV) midazolam 0.015mg/kg in a volume of 5 ml normal saline, followed by IV fentanyl 1µg/kg in a volume of 5 ml normal saline. In group M, patients received pretreatment with IV midazolam 0.03mg/kg in a volume of 5 ml normal saline, followed by 5ml of IV normal saline. The test drug was injected over 30 s, and after 120 s, IV etomidate 0.3 mg/kg was injected over 30 s. The patients were observed for 120 s for myoclonus and graded as mild, moderate, or severe. Heart rate, blood pressure, and oxygen saturation were recorded immediately after test drug injection and at every minute for 5 min.

Results: The demographic parameters and hemodynamic parameters were comparable between the two groups. In group M, the incidence of myoclonus was 36.67% (26.67% mild and 10% moderate) whereas, in the group MF, the incidence of myoclonus was 26.67% (3.33% mild, 16.67% moderate, and 6.67% severe). This incidence of myoclonus was significantly lower in group MF ($p=0.030$).

Conclusions: The incidence of etomidate-induced myoclonus is significantly lower in patients pretreated with midazolam and fentanyl combination as compared to midazolam alone.

Trial registration: Clinical Trial Registry Details: [CTR/2019/05/018920](https://www.clinicaltrials.gov/ct2/show/study?term=CTR/2019/05/018920)

Keywords: Etomidate, Fentanyl, Midazolam, Myoclonus

Background

Etomidate is a carboxylated imidazole-containing compound that was introduced as an anesthetic induction agent (Gupta & Gupta, 2018). It is used as an alternative to propofol, especially in the presence of an unstable cardiovascular system due to its relatively large safety

margin for hemodynamic stability because it does not affect the sympathetic nervous system and function of the baroreceptors (Ali, 2019). But it is associated with various side effects; primarily adrenocortical suppression and pain on injection, postoperative nausea and vomiting, increase in intraocular pressure, myoclonus, and hiccups (Gupta & Gupta, 2018).

Myoclonus is reported to occur in 50–80% of patients receiving etomidate in the absence of pretreatment (Gupta

* Correspondence: drupesh.yadav98@gmail.com

Department of Anaesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India

& Gupta, 2018). Myoclonus is defined as sudden, brief, involuntary jerking of a muscle or group of the muscles, either irregular, or rhythmic (Faught, 2003). In some patients, there can be serious consequences of this side effect, e.g., non-fasted emergency patients carry the risk of regurgitation and aspiration, open globe injuries are at high risk of prolapse of vitreous material.

There have been studies regarding the use of various other drugs like remifentanyl, ketamine also for the prevention of etomidate-induced myoclonus (EIM) (Schwarzkopf et al., 2003; Hwang et al., 2008; Wu et al., 2016). While a study comparing midazolam with the control group suggested a 50% decrease in the incidence of EIM with midazolam, (Schwarzkopf et al., 2003) another study suggested a 40% decrease in EIM using midazolam (Hüter et al., 2007). Very few studies (Prakash et al., 2019; Isitemiz et al., 2014) have used a combination of fentanyl and midazolam, which is important to minimize any hemodynamic changes due to the individual drugs used to prevent myoclonus associated with etomidate. Though they have reported a decreased incidence of etomidate-induced myoclonus in those patients receiving the combination, the results from these studies are not conclusive regarding the best option to prevent etomidate-induced myoclonus.

Midazolam and fentanyl (one or both) are essential components of induction of anesthesia, and we can use these essential drugs (fentanyl and/or midazolam followed by induction doses of etomidate after 2 min of wait period to allow the onset of action of midazolam and/or fentanyl) to decrease the incidence of EIM and it can avoid the use of concomitant use of other drugs for prevention of EIM

The aim of the study was to evaluate the efficacy of pretreatment with low-dose midazolam and fentanyl and midazolam alone in reducing the occurrence of etomidate-induced myoclonus in patients for surgery under general anesthesia.

Methods

This double-blinded randomized active-controlled comparative study was conducted after the approval from the institutional ethics committee and registration with the clinical trial registry of India (CTRI/2019/05/018920) between November 1, 2019, to March 31, 2020, in a tertiary care central government institute. Patients of either sex, age between 18 and 65 years belonging to the American Society of Anesthesiologists (ASA) Grades I and II posted for elective surgery under general anesthesia were included in this study. Patient with a history of any neurological disease, adrenal cortical dysfunction, history of allergy to study drugs, and those having received any sedative within the previous 24 h—pregnant or lactating women were excluded.

The sample size was calculated based on a previous study (Dey & Kumar, 2018) which observed that the occurrence of myoclonus in the group receiving midazolam was 62.5%. Taking this value as a reference and assuming a difference of 40% of myoclonus occurrence between midazolam alone and midazolam and fentanyl combined, the minimum required sample size with 90% power of study and 5% level of significance was 27 patients in each study group. So a total sample size taken was 60 (30 patients per group).

After a thorough pre-operative evaluation the patients were randomly allocated into two groups, of 30 patients each, using computer-generated random numbers. Randomization and group allocation were done by an independent anesthesiologist who was not part of the study. Allocation concealment was done using a sequentially numbered sealed opaque envelope technique. Written informed consent was taken a day before surgery.

In the operation theatre, standard monitors like non-invasive blood pressure, pulse oximeter, and 5 lead electrocardiogram were attached and baseline parameters were recorded. An 18 G intravenous catheter was inserted on the dorsum of the hand and ringer lactate infusion was started. While being pre oxygenated with 100% oxygen, patients were administered drugs used for the study based on the group he/she was assigned to the following:

Group MF

The patients received pretreatment with intravenous (IV) midazolam 0.015mg/kg in a volume of 5 ml normal saline, followed by IV fentanyl 1µg/kg in a volume of 5 ml normal saline.

Group M

The patients received pretreatment with IV midazolam 0.03mg/kg in a volume of 5 ml normal saline, followed by 5ml of IV normal saline.

The test drug (midazolam with fentanyl combination or midazolam alone) was injected over 30 s, and after 120 s, IV etomidate 0.3 mg/kg was injected over 30 s. The patients were observed for 120 s for myoclonus by an independent observer who was not part of the study team and was blinded to the group allocation. Then, IV vecuronium bromide 0.1 mg/kg was administered. Heart rate, blood pressure, and oxygen saturation were recorded immediately after test drug injection and at every minute for 5 min at which point the study period ended. Following this, IV fentanyl 2 µg/kg was given to group M and IV fentanyl 1 µg/kg was given to the group MF as boluses to complete the analgesic dose of IV fentanyl. Tracheal intubation was performed and anesthesia was maintained using 1 MAC sevoflurane in 50:50 O₂ and

N₂O. At the end of the surgery, the neuromuscular blockade was reversed using Inj. Neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01 mg/kg.

Myoclonus is an involuntary action, short contraction of few muscle fibers or whole muscle, leading to a transient movement of the body part. The occurrence and severity of myoclonus were graded by the scale given by Doenicke et al. (Doenicke et al., 1999) where the movement of a short movement of a body segment like finger or shoulder (mild myoclonus), movement of two different muscles or muscle groups of the body, e.g., face and leg (moderate myoclonus) and intense clonic movement in two or more muscle groups like fast abduction of a limb (severe myoclonus).

The hemodynamic parameters like pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were noted at baseline, 1 min, 2 min, 3 min, 4 min, and 5 min after giving the test drugs.

In statistical analysis, categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. The normality of data was tested by the Kolmogorov-Smirnov test. If the normality is rejected, then a non-parametric test was used.

Quantitative variables were compared using the unpaired *t* test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups. The qualitative variable was compared using the chi-square test/Fisher’s exact test. A *p* value of <0.05 was

considered statistically significant. The data were analyzed using the Statistical Package for Social Sciences (SPSS, IBM) version 21.0.

Results

A total of 69 patients were assessed for eligibility, and 60 patients were recruited and all completed the study as mentioned in the consort diagram (Fig. 1). There was a statistically similar gender distribution, body weight (in kg), and ASA grade in both groups. The mean age in group MF was 33.97 ± 13.4 years and in the group, M was 41.6 ± 16.68 years and statistically similar (Table 1). Fisher’s exact test was used to assess the incidence and severity of EIM. There was a significant difference in the incidence and severity of myoclonus between the two groups. In group M, the incidence of myoclonus was 36.67% which comprised of 26.67% mild, 10% moderate, and 0% severe myoclonus while in the group MF, the incidence of myoclonus was 26.67% which comprised 3.33% mild, 16.67% moderate, and 6.67% severe degree of myoclonus and difference between two groups was statistically significant (*p*=0.030) (Table 2).

Mann-Whitney *U* test or Student’s *t* test was used as applicable to analyze the hemodynamic parameters. There was no significant difference between the variations in the pulse rate at various time intervals among the patients in both groups.

There was a fall in SBP, DBP, and MBP from baseline in the group M as well as in the group MF after administration of test drugs. However, falls in all blood

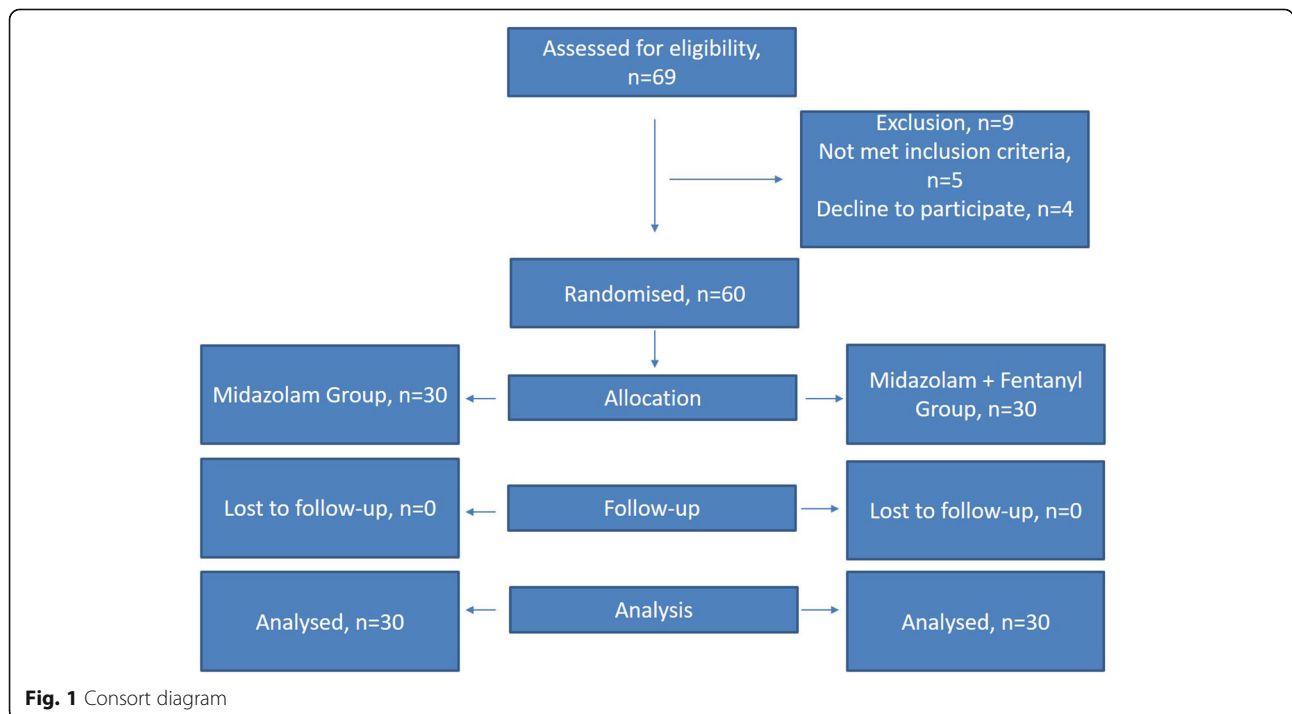


Fig. 1 Consort diagram

Table 1 Demographic details of both groups

		Group MF* (n=30) Number (percentage)	Group M† (n=30) Number (percentage)	P value
Age in years, mean±SD‡ (angle)		33.97 ± 13.4 (19–61)	41.6 ± 16.68 (18–75)	0.088
Age distribution in years	≤20	5 (16.67)	2 (6.67)	0.320
	21–30	11 (36.67)	8 (26.67)	
	31–40	6 (20)	3 (10)	
	41–50	4 (13.33)	7 (23.33)	
	51–60	3 (10)	7 (23.33)	
	>60	1 (3.33)	3 (10)	
Gender	Male	17 (56.67)	17 (56.67)	1.00
	Female	13 (43.33)	13 (43.33)	
ASA grade	I	15 (50)	19 (63.33)	0.297
	II	15 (50)	11 (36.67)	
Body weight in kg Mean±SD‡ (range)		62.13 ± 6.93 (48–73)	63.1 ± 8.1 (48–78)	0.603

Chi-square test, Fisher's exact test and Mann-Whitney *U* test were used to analyze the demographic parameters

*MF Midazolam with Fentanyl, †M Midazolam, ‡SD Standard Deviation

pressure, SBP, DBP, and MBP were comparable in both groups. The hemodynamic parameters up to 5 min after giving test drugs are shown in Fig. 2. There was no difference in oxygen saturation in both groups throughout the study in both groups at all-time intervals.

Discussion

In our study, we had chosen midazolam doses 0.015 mg/kg IV. We had observed the occurrence of EIM for 120 s, and it was based on previous studies in which they observed myoclonus from 90 s to even 10 min, but most of the EIM occurred within 120 s (Schwarzkopf et al., 2003; Hwang et al., 2008; Hüter et al., 2007; Prakash et al., 2019; Isitemiz et al., 2014; Dey & Kumar, 2018; Doenicke et al., 1999; Khteishat et al., 2011; Aktolga et al., 2010; Yang et al., 2000).

Various studies have taken midazolam doses ranging from 0.015 to 0.5 mg/kg, and most of the studies have taken 0.015 mg/kg which is the minimum effective dose

for sedation as well as prevention of EIM (Schwarzkopf et al., 2003; Hwang et al., 2008; Hüter et al., 2007; Prakash et al., 2019; Isitemiz et al., 2014; Dey & Kumar, 2018; Doenicke et al., 1999; Khteishat et al., 2011; Aktolga et al., 2010; Yang et al., 2000). We found that the incidence of EIM in patients pretreated with 0.015mg/kg midazolam and 1 µg/kg fentanyl was significantly less than in those patients pretreated with 0.03mg/kg midazolam; however, the severity of myoclonus was higher.

The total incidence of myoclonus in the midazolam group was 36.67% while in the midazolam along with fentanyl group was 26.67%. The higher severity of EIM in midazolam along with the fentanyl group is in contrast to a previous study (Prakash et al., 2019) and the reason cannot be explained.

Though the exact mechanism of action is not clear, it may be because of subcortical disinhibition that normally suppresses extrapyramidal motor activity, or due

Table 2 Incidence and severity of myoclonus in both groups

Myoclonus grade	Group MF (n=30) Number (percentage)	Group M (n=30) Number (percentage)	Total Number (percentage)	P value
None	22 (73.33)	19 (63.33)	41 (68.33)	0.030
Mild	1 (3.33)	8 (26.67)	9 (15)	
Moderate	5 (16.67)	3 (10)	8 (13.33)	
Severe	2 (6.67)	0 (0)	2 (3.33)	
Total	30 (100)	30 (100)	60 (100)	

Fisher's exact test was used to calculate the incidence and severity

*MF Midazolam with Fentanyl, †M Midazolam

The occurrence and severity of myoclonus were graded in none, mild, moderate, and severe. A short movement of a body segment like finger or shoulder (mild myoclonus), movement of two different muscles or muscle groups of the body, e.g., face and leg (moderate myoclonus) and intense clonic movement in two or more muscle groups like fast abduction of a limb (severe myoclonus)

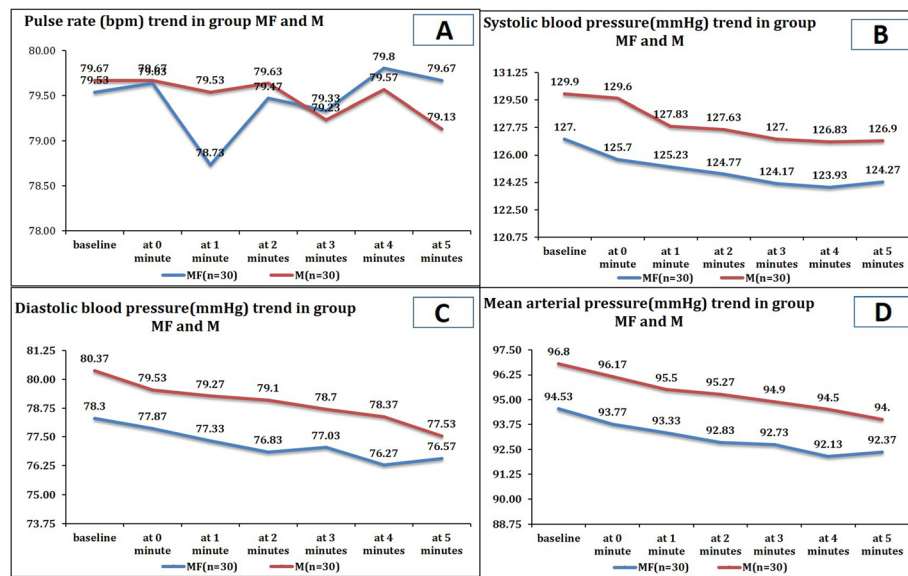


Fig. 2 Hemodynamic parameters, **A** showing pulse rate, **B** showing systolic blood pressure, **C** showing diastolic blood pressure, and **D** showing mean blood pressure at various periods in midazolam with fentanyl (FM) group and midazolam alone (M) group

to lower concentration of inhibitory neuronal circuits and at lower concentrations than the excitatory circuits (Doenicke et al., 1999; Gancher et al., 1984). Yet another potential mechanism may be that etomidate acts on the gamma-aminobutyric acid (GABA)_A receptor leading to inhibition of the central nervous reticular activating system. Due to inhibition of neurotransmission through GABA_A receptor activation, there may be the skeletal muscle control of relevant signal transmission which allows the occurrence of autonomic nervous conduction (Doenicke et al., 1999; Gancher et al., 1984). EEG observations showing non-seizure phenomena like isolated, rapid, sharp transients may be seen during the myoclonus but epileptic paroxysms or ictal spiking is not seen, therefore suggesting a lack of epileptogenic foci for these myoclonic movements (Doenicke et al., 1999).

EIM can be prevented by pre-treatment with benzodiazepines or fentanyl, which inhibit subcortical neuronal activity. Benzodiazepine (midazolam) with or without opioids (fentanyl) decrease the occurrence of EIM by causing the central nervous system inhibition, by their action on different receptors. Fentanyl causes the stimulation of μ receptors on GABA-nergic neurons in the basal ganglia and also decreases the incidence of EIM (Prakash et al., 2019).

Many previous studies have shown conflicting results regarding the role of midazolam pretreatment on its efficacy in reducing EIM. In a recent meta-analysis, it was reported that midazolam can effectively decrease the occurrence of EIM as well as the severity of EIM (Zhou et al., 2017). Some studies show the incidence of EIM

following midazolam pre-treatment to range from 10 to 20% (Schwarzkopf et al., 2003; Hwang et al., 2008; Hüter et al., 2007; Khteishat et al., 2011). Wang et al. reported only mild EIM in patients pretreated with 0.05mg/kg midazolam with an incidence of 17%. Patel et al. reported a 40% incidence of EIM in patients premedicated with 0.05mg/kg midazolam and the absence of severe myoclonus (Hwang et al., 2008). Aktolga et al. also reported a 37% incidence of EIM and no incidence of severe myoclonus in patients pretreated with midazolam 0.05mg/kg (Aktolga et al., 2010).

Opioids have been demonstrated in various studies to decrease the incidence of EIM. Pretreatment with fentanyl 2 μ g/kg resulted in an incidence of EIM of 5.6% and 6.7% (Khteishat et al., 2011; Yang et al., 2000) while in another study, fentanyl 100 μ g was found to be ineffective in decreasing EIM (Fassoulaki et al., 1987). Stockham et al., using three doses of fentanyl, demonstrated that patients receiving fentanyl 500 μ g experience apnea but no myoclonus compared to patients receiving 100 μ g fentanyl with a 33% incidence of myoclonus (Stockham et al., 1998).

There are only a few studies in the current literature that compare midazolam with a combination of midazolam and fentanyl as premedication to prevent etomidate-induced myoclonus.

Prakash et al. (Prakash et al., 2019) reported 48.6%, 78.6%, and 15.7% incidence of EIM in patients receiving pretreatment with 2 μ g/kg fentanyl, 0.03mg/kg midazolam, and a combination of 2 μ g/kg fentanyl and 0.03mg/kg midazolam, respectively. Their finding regarding the

lower incidence of EIM in the fentanyl and midazolam group is consistent with our findings. However, in contrast to their study, we found no incidence of severe myoclonus in the midazolam-only group.

Isitemiz et al. (Isitemiz et al., 2014) reported 85%, 40%, 70%, and 25% incidence of EIM in the control group, 1µg/kg of the fentanyl group, 0.03mg/kg of the midazolam group, and a combination of 0.5µg/kg of fentanyl and 0.015mg/kg of the midazolam group, respectively. Those patients who received fentanyl premedication and those who received midazolam both had an incidence of 25% mild and moderate myoclonus, but the incidence of severe myoclonus was high in those patients in the midazolam group (45%) than the fentanyl group (15%). They have reported a decrease in myoclonus when both fentanyl and midazolam were given as premedication which is similar to our findings. In their study, the incidence of myoclonus in the midazolam-only group is higher than seen in our study, with increased severity as well.

While the incidence of myoclonus in our study was 36.67% following pre-treatment with midazolam 0.03 mg/kg administered 2 min before etomidate, there are other reports which have noted the ineffectiveness of midazolam in reducing EIM. Sedighinejad et al. used 0.015mg/kg midazolam in a study comparing different drugs to prevent EIM and found that the incidence in the midazolam group to be 71.85% out of which 58.8% was severe myoclonus (Sedighinejad et al., 2016). Wasinwong et al. too had similar results with midazolam pre-treatment before induction with etomidate. There was a 78% incidence of myoclonus in patients who were given 0.03mg/kg midazolam as pretreatment (Wasinwong et al., 2011).

The differences in our results from those of previous authors may be related to differences in the dosage and timing of administration of pre-treatment agents, the rate of administration of etomidate, and population characteristics. Contrary to our findings, Isitemiz et al. found that the mean arterial pressure measurements were significantly lower in patients who were given a combination of midazolam and fentanyl as premedication as compared to those patients who received only midazolam and those who were not given any premedication (Isitemiz et al., 2014).

Our study has certain limitations, we only included ASA I/II patients, so further studies may be required to assess EIM in patients with significant comorbidities and adverse events that may occur as a result. We also did not compare different doses of midazolam, which could have brought clarity regarding the ideal dose of midazolam for the prevention of etomidate-induced myoclonus without causing significant variation in hemodynamic parameters.

Conclusions

The incidence of etomidate-induced myoclonus is significantly lower, but the severity is more when midazolam along with fentanyl is given as pretreatment as compared to pretreatment with midazolam 2 min (120 s) before induction doses of etomidate.

Abbreviations

ASA: American Society of Anesthesiology; DBP: Diastolic blood pressure; EIM: Etomidate-induced myoclonus; GABA: Gamma-aminobutyric acid; IV: Intravenous; MBP: Mean blood pressure; PR: Pulse rate; SBP: Systolic blood pressure

Acknowledgements

We acknowledge the Department of Anaesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences, and Dr. RML Hospital, New Delhi, for help and smooth conduct of the study.

Authors' contributions

KH worked on the idea, design, study protocol writing, study conduction, analysis, and interpretation of the data. NK helped in the design, study conduction, analysis of data, and manuscript writing and revision. RY helped in the design, study conduction, manuscript writing, editing, revision, and proofreading. The authors have read and approved the final manuscript.

Funding

This study did not include any funding source.

Availability of data and materials

Data can be made available on written request by any competent authority.

Declarations

Ethics approval and consent to participate

The approval was taken from the Institutional Ethics Committee of the Atal Bihari Vajpayee Institute of Medical Sciences and Dr. RML Hospital, New Delhi, India, with reference no. TP (MD/MS) (28/2018)/IEC/PGIMER/RMLH/1862 dated October 24, 2018, and written informed consent was taken from all the participants to enroll in this study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Received: 14 January 2021 Accepted: 29 August 2021

Published online: 19 September 2021

References

- Aktolga S, Gunes Y, Gündüz M, Isik G (2010) A comparison of midazolam and dexmedetomidine for the prevention of myoclonic movements and pain following etomidate injection. *J Anaesth Clin Pharmacol*. 26:162–166
- Ali Z (2019) Intraoperative neurophysiologic monitoring and anaesthetic implications. *Indian J Anaesth* 63(2):81–83. https://doi.org/10.4103/ija.IJA_64_19
- Dey S, Kumar M (2018) 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 Anaesth Clin Pharmacol* 34:94–98
- Doenicke A, Roizen M, Kugler J, Kroll H, Foss J, Ostwald P (1999) Reducing myoclonus after etomidate. *Anesthesiology*. 90(1):113–119. <https://doi.org/10.1097/0000542-199901000-00017>
- Fassoulaki A, Pateras C, Kaniaris P (1987) Fentanyl in the prevention of etomidate-induced myoclonus. *Cah Anesthesiol* 35(3):201–202
- Faught E (2003) Clinical presentations and phenomenology of myoclonus. *Epilepsia* 44(Suppl 11):7–12. <https://doi.org/10.1046/j.1528-1157.44.s11.3.x>
- Ganchar S, Laxer K, Krieger W (1984) Activation of epileptogenic activity by etomidate. *Anesthesiology*. 61(5):616–617. <https://doi.org/10.1097/0000542-198411000-00029>

- Gupta P, Gupta M (2018) Comparison of different doses of intravenous lignocaine on etomidate-induced myoclonus: a prospective randomised and placebo-controlled study. *Indian J Anaesth* 62(2):121–126. https://doi.org/10.4103/jja.563_17
- Hüter L, Schreiber T, Gugel M, Schwarzkopf K (2007) Low-dose intravenous midazolam reduces etomidate-induced myoclonus: a prospective, randomized study in patients undergoing elective cardioversion. *Anesth Analg*. 105(5):1298–1302. <https://doi.org/10.1213/01.ane.0000287248.25610.c0>
- Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, Han SH (2008) A comparison of midazolam with remifentanyl for the prevention of myoclonic movements following etomidate injection. *J Int Med Res*. 36(1):17–22. <https://doi.org/10.1177/147323000803600103>
- Isitemiz I, Uzman S, Toptaş M, Vahapoglu A, Gül YG, Inal FY, Akkoc I (2014) Prevention of etomidate-induced myoclonus: which is superior: fentanyl, midazolam, or a combination? A Retrospective comparative study. *Med Sci Monit*. 20:262–267. <https://doi.org/10.12659/MSM.889833>
- Khteishat B, Salaytah W, Qatawneh T, Alsagheer M (2011) The effect of preinduction with midazolam, fentanyl, and ketamine on etomidate induced myoclonic muscle movements. *J Royal Med Services* 18:38–41
- Prakash S, Mullick P, Virmani P, Talwar V, Singh R (2019) Effect of pre-treatment with a combination of fentanyl and midazolam for prevention of etomidate-induced myoclonus. *Turk J Anaesthesiol Reanim*. <https://doi.org/10.5152/TJA.R.2019.90248>
- Schwarzkopf K, Hueter L, Simon M, Fritz H (2003) Midazolam pretreatment reduces etomidate-induced myoclonic movements. *Anaesth Intensive Care*. 31(1):18–20. <https://doi.org/10.1177/0310057X0303100103>
- Sedighinejad A, Naderi Nabi B, Haghighi M, Biazar G, Imantalab V, Rimaz S, Zaridoost Z (2016) Comparison of the effects of low-dose midazolam, magnesium sulfate, remifentanyl and low-dose etomidate on prevention of etomidate-induced myoclonus in orthopedic surgeries. *Anesth Pain Med*. 6(2):e35333. <https://doi.org/10.5812/aapm.35333>
- Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F, Hilkens P (1998) Fentanyl pretreatment modifies anesthetic induction with etomidate. *Anaesth Intensive Care* 16(2):171–176. <https://doi.org/10.1177/0310057X8801600207>
- Wasinwong W, Uakritdathikar T, Kovitwanawong N, Pakam P (2011) Prevention of etomidate-induced myoclonic movement after midazolam co-induction with low-dose etomidate. *Songklanagarind Med J*. 29:1–9
- Wu GN, Xu HJ, Liu FF, Wu X, Zhou H (2016) Low-dose ketamine pretreatment reduces the incidence and severity of myoclonus induced by etomidate: a randomized, double-blinded, controlled clinical trial. *Medicine (Baltimore)* 95:e2701
- Yang YY, Choi SJ, Kim HJ, Son SC (2000) The effect of midazolam, fentanyl and a small dose of etomidate for prevention of myoclonus during induction of anesthesia with etomidate. *Korean J Anesthesiol* 39(2):166–171. <https://doi.org/10.4097/kjae.2000.39.2.166>
- Zhou C, Zhu Y, Liu Z, Ruan L (2017) Effect of pretreatment with midazolam on etomidate-induced myoclonus: a meta-analysis. *J Int Med Res*. 45(2):399–406. <https://doi.org/10.1177/0300060516682882>

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)
