



ORIGINAL INVESTIGATION

Comparison of the influence of low dose etomidate and propofol as priming dose on the incidence of etomidate induced myoclonus: a randomised, double-blind clinical trial

Srilata Moningi, G. Poojitha Reddy, Sapna Annaji Nikhar *, Ramakrishna Chikkala, Dilip Kumar Kulkarni, Gopinath Ramachandran

Nizam's Institute of Medical Sciences, Department of Anaesthesia and Intensive Care, Hyderabad, India

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KEYWORDS

Myoclonus;
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Abstract

Background: Though hemodynamically stable, etomidate is known for its myoclonus side effect following induction. The main aim of this study is an effective attempt to decrease the incidence of myoclonus with a priming agent.

Methods: A prospective, double-blind study was carried out on 50 adults posted for elective surgery. After premedication, priming was done with etomidate 0.03 mg.kg^{-1} (Group E) and propofol 0.2 mg.kg^{-1} (Group P), i.e., 1/10th of induction dose. After 60 seconds of priming, patients were induced with etomidate by titrating dose over 60 seconds until loss of verbal command and eyelash reflex. The grading of myoclonus, induction dosage, and hemodynamics for 10 minutes post induction were recorded.

Results: In the study, only 4 cases had myoclonus. Grade 1 myoclonus was encountered in three cases of etomidate group, while only one case in the propofol group had grade 2 myoclonus which was not statistically significant (p -value: 0.12). There was a significant reduction in the etomidate induction dosage in both groups.

Conclusion: Priming with etomidate and propofol is equally effective in reducing myoclonus with the added benefit of hemodynamic stability and reduction of an induction dose of etomidate (> 50%).

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* Corresponding author.

E-mail: sapnanikhar@gmail.com (S.A. Nikhar).

Introduction

Etomidate as compared with other induction agents is associated with less hemodynamic changes, less pain during injection with lipid formulation,¹ less histamine release, and high therapeutic index.² Therefore, etomidate is the preferred induction agent for rapid sequence induction during emergency situations in view of hemodynamic instability.³ Etomidate use has been limited since it has shown to cause adrenocortical suppression, myoclonus, and pain on injection.³ Single-induction dose of etomidate has not shown any deleterious effects; rather, hemodynamic stability has increased due to its usage in the intraoperative management of emergency and sick cardiac cases. Thus, etomidate has seen a resurgence in its usage in anesthesia practice. Myoclonus, the side effect of etomidate is not desired in situations where there are closed globe injuries to eye and penetration trauma of the abdomen. Prevention of myoclonus by pretreatment with midazolam, magnesium sulphate, opioids, gabapentin, ketamine, propofol, and priming dose of etomidate has been studied.⁴⁻⁷ Both etomidate and propofol in induction dosages are known to cause myoclonus. Etomidate in low priming doses and propofol in different doses has been studied for the prevention of myoclonus induced with etomidate induction. But none of the studies compared etomidate with propofol. This study attempted to compare myoclonus incidence with a priming dose of etomidate, and propofol as both the drugs in induction dosage is known to cause myoclonus.⁸

Methods

The study is registered in the Clinical Trial Registry of India. REF/2015/03/008627. The study has approval from NIEC [NIMS (Nizam's Institute of Medical Sciences, Hyderabad) Institutional ethical committee] with approval no. EC/NIMS/1672/2015. After ethics committee approval and informed consent of patients, 50 American Society of Anesthesiologists (ASA) I and II physical status patients, of either sex, aged between 20 to 65 years, with Mallampati grading I and II, scheduled for lumbar laminectomy under general anaesthesia were prospectively enrolled in the study. Patients were randomly allocated in two groups. This was accomplished with RAND (0,1) [Microsoft. (2010). Microsoft Excel [computer software] Redmond, Washington], and the study was conducted in a double-blind fashion. Patients with a history of epilepsy, alcoholics, those with endocrine disorders – Cushing's syndrome, pituitary disorders, and immunosuppressed patients were excluded.

This study adhered to CONSORT guidelines (<http://www.consort-statement.org>). The study drugs were prepared by an anesthesia technician who was aware of the randomization number allotted and the demographic profile of the patient. The study participants and investigator collecting the data were blinded to the treatment group. Baseline parameters heart rate (HR), blood pressure (BP), oxygen saturation by pulse oximetry (SPO₂), and entropy were noted. All patients were premedicated with midazolam 0.02 mg.kg⁻¹ + fentanyl 2 µg.kg⁻¹ intravenously. The above parameters were again noted after 5 minutes of premedication. Patients were ventilated with 100% oxygen

if SPO₂ falls to < 97% or the patient becomes apneic. After 5 minutes of premedication, etomidate (E) group of patients received priming dose of etomidate 0.03 mg.kg⁻¹ and propofol (P) group of patients with 0.2 mg.kg⁻¹ (1/10th of induction dose). After 60 seconds of priming, patients were induced with etomidate by titrating dose over 60 seconds until loss of verbal command and eyelash reflex. Entropy was used for monitoring depth of anesthesia. Patients were observed during induction and 1 minute following induction for myoclonus and grades of myoclonus. This was the primary objective of the study. The myoclonus grades used were⁹: Grade 0, no myoclonus; Grade 1, mild myoclonus (Small movements in 1 body segment, such as finger or wrist); Grade 2, moderate myoclonus (Slight movements in 2 or more muscle areas, such as face or shoulder); Grade 3, severe myoclonus (intense movements in 2 or more muscle areas, sudden adduction of an extremity). The dose of etomidate required for each patient for loss of verbal command and eyelash reflex was noted.

After confirming for mask ventilation, neuromuscular blockade was achieved with atracurium 0.5 mg.kg⁻¹, and trachea was intubated with an appropriate sized endotracheal tube around 4 minutes after induction. Entropy was maintained between 40–60 following induction for 10 minutes. The ventilation was done with 100% O₂, and blood pressure and heart rate were recorded every 1 minute till 10 minutes following induction. The supplemental doses of etomidate were used to intubate if entropy was more than 60. The endpoint of the study was 10 minutes past induction after recording the hemodynamic parameters. The post inclusion exclusion criteria included patients with an unanticipated difficult airway sustained tachycardia or rise in BP (> 40% baseline), bradycardia (< 50 bpm) requiring atropine, and hypotension requiring vasopressor administration.

The primary objective of this study was to compare the incidence of myoclonus and its severity with a priming dose of etomidate, and propofol during induction with etomidate. The secondary objectives included the induction dosage of etomidate and hemodynamic changes following induction.

Statistical analysis

Sample sizes of 21 in group 1 and 21 in group 2 achieved to detect a non-inferiority margin difference between the group proportions of -0.3000. The reference group proportion is 0.5000. The treatment group proportion is assumed to be 0.2000 under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion is 0.6000. The test statistic used is the one-sided Z test (unpooled). The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is 0.0542. As dropout of cases would be expected, the total sample size of 50 (25 in each group) was taken for undertaking this study. PASS software (PASS 13 Power Analysis and Sample Size Software (2014). NCS, LLC. Kaysville, Utah, USA, ncss.com/software/pass) was used for estimating the sample size for conducting this study.

NCSS version 9 statistical software (NCSS 9 Statistical Software (2013). NCS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.) was used for statistical analysis. Data was presented as the mean (± S.D). Categorical data

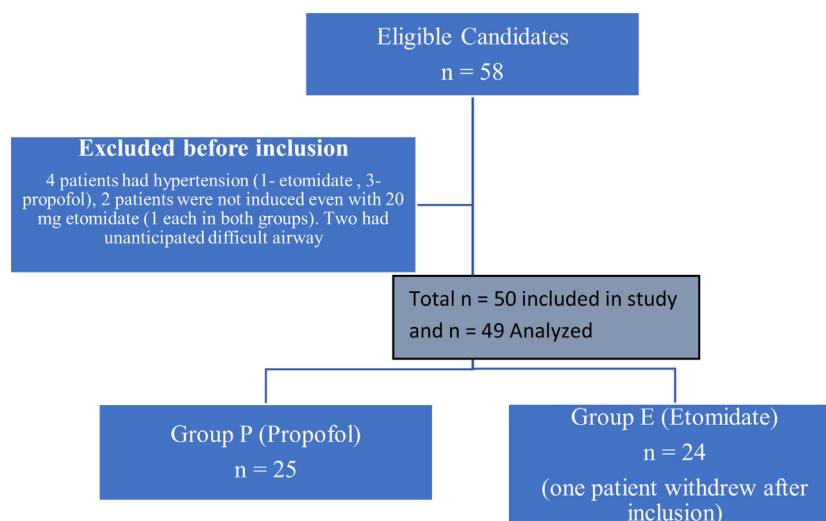


Figure 1 Flow chart of participants in the study.

was described as the number of patients (n). Normality of the data was tested using the Kolmogorov-Smirnov test. Categorical variables were compared with the chi-square test. Continuous variables were compared using independent sample *t*-test. Within the group and intergroup comparison of hemodynamic variables was done using ANOVA. A *p*-value < 0.05 was considered as significant.

Results

Fifty adults aged 20 to 65 years were studied. One patient who was randomly allotted to etomidate group voluntarily withdrew from the study after inclusion (Fig. 1), thus only 49 were analyzed. The demographic data was comparable in both groups (Table 1). The propofol group had 5 ASA II patients (20%), and etomidate group had only one ASA II patient (4.16%) with *p*-value of 0.05. There was no significant difference in state entropy (SE) and response entropy (RE) in between the two groups (baseline, 5 minutes following premedication and following induction). This suggests that the depth of anesthesia was maintained in both groups without significant difference. The data was found to be normally distributed with respect to demographic and other control parameters.

After induction, 3 patients (12.5%) in the etomidate group had myoclonus of grade 1, and 1 patient (4%) in the propofol group had myoclonus of grade 2 (Fig. 2). Overall, only 4 patients had myoclonus out of 49 included (8.16%). There was no significant difference between the groups (*p* = 0.12). The dose of etomidate needed for loss of eyelash reflex was 3.96 ± 1.62 mg, and 4.42 ± 2.12 mg in propofol and etomidate group respectively (*p*-value 0.40). Similarly, the dose of etomidate needed for loss of verbal commands was 3.98 ± 1.86 , and 4.40 ± 1.63 mg in propofol and etomidate group, respectively (0.88) as shown in Table 2.

The changes in heart rate and MAP were comparable between the groups (*p* = 0.8) and also within the groups (Figs. 3 and 4).

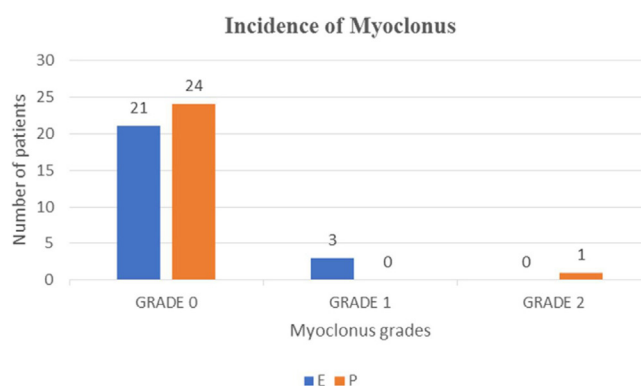


Figure 2 Incidence of myoclonus occurrence in the two groups. E, Group etomidate; P, Group propofol (*p* = 0.12).

Discussion

Our study findings did not reject the null hypothesis, thus stating that both etomidate and propofol in low doses are effective in attenuating the myoclonic movements following induction with etomidate. Only 4 patients out of 50 had myoclonus (8.16%).

In the study by Isitemiz et al., the incidence of myoclonus was reduced significantly with fentanyl 1 mcg.kg^{-1} (40%) and the combination of midazolam 0.15 mg.kg^{-1} + fentanyl 0.5 mcg.kg^{-1} (25%).^{9,10} The incidence of myoclonus with a combination of midazolam and fentanyl was 25%, which is quite high and still distressing for any patient. Fentanyl is routinely used as an analgesic as a standard protocol in all the recentres, including ours. Induction with etomidate with fentanyl as an analgesic used in routine basis showed a significant increase in the incidence. A trial study was conducted with fentanyl 2 mcg.kg^{-1} and midazolam 0.02 mg.kg^{-1} , and noticed a significant incidence of myoclonus almost with all the cases which appeared ethically unacceptable. The intensity of pain with a priming dose of propofol injection is expected to be less, and this combination was helpful in combating this.¹¹ Hence, to avoid this bias, we standardized

Table 1 Comparison of demographic and control parameters in both groups.

Variable	Mean \pm SD Group P (n = 25)	Mean \pm SD Group E (n = 24)	p-value
Age	37.32 \pm 9.07	38.79 \pm 10.79	0.6
Sex			
Male	13 (52%)	11 (45.83%)	0.77
Female	12 (48%)	13 (54.16%)	
Height (cm)	162 \pm 10.3	157 \pm 13.1	0.2
Weight (kg)	63.28 \pm 10.6	61 \pm 9.4	0.44
ASA			
I	20 (80%)	23 (95.83%)	0.05
II	5 (20%)	1 (4.16%)	
Response entropy (baseline)	96.9 \pm 2.03	97.2 \pm 2.1	0.67
State entropy (baseline)	88.24 \pm 2.5	88.3 \pm 4.2	0.86
Response entropy (5 min after premed)	93 \pm 3.456.07	93.3 \pm 7	0.34
State entropy (5 min after premed)	84.7 \pm 5.5	85.8 \pm 6.4	0.5
Response entropy (induction)	54.24 \pm 14.4	50.7 \pm 13.4	0.37
State entropy (induction)	51.8 \pm 14.4	48.4 \pm 14.6	0.4

SD, standard deviation; P, propofol group; E, etomidate group.
Data represented as n or mean \pm SD.

Table 2 Induction dose in both the groups.

Dose	Group P	Group E	p-value
Loss of eyelash reflex in mg \pm SD (mg.kg ⁻¹ \pm SD)	3.96 \pm 1.62 (0.06 \pm 0.03)	4.42 \pm 2.12 (0.07 \pm 0.04)	0.40 0.3
Loss of verbal commands in mg \pm SD (mg.kg ⁻¹ \pm SD)	3.98 \pm 1.86 (0.07 \pm 0.03)	4.40 \pm 1.63 (0.07 \pm 0.03)	0.4 0.3

SD, standard deviation.
Data represented as n or mean \pm SD.

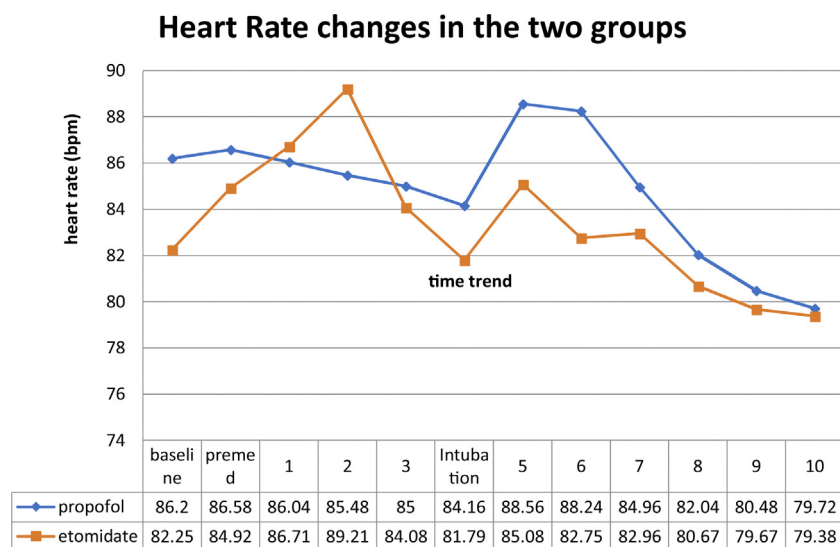


Figure 3 Heart rate changes in the two groups. Premed, 5 minutes following premedication; 1, 1 minute following induction; 2, 2 minutes following induction; 3, 3 minutes following induction; 5, 5 minutes following induction; 6, 6 minutes following induction; 7, 7 minutes following induction; 8, 8 minutes following induction; 9, 9 minutes following induction; 10, 10 minutes following induction.

the combination of midazolam and fentanyl as a premedication regime for both the groups along with study drugs for conducting this study.

Etomidate, the preferred agent for induction in view of hemodynamic stability,¹² myoclonus the main side effect associated with its use cannot be neglected.¹³ The incidence

Mean Arterial Pressure Trends in the two groups

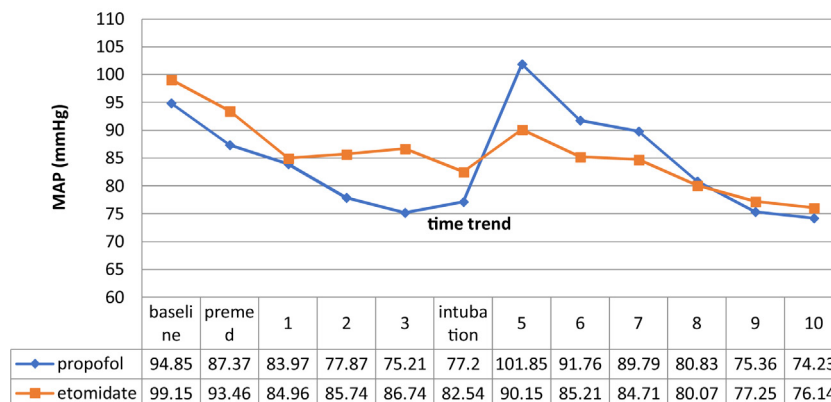


Figure 4 Mean arterial pressure trends in the two groups. MAP, mean arterial pressure; premed, 5 minutes following premedication; 1, 1 minute following induction; 2, 2 minutes following induction; 3, 3 minutes following induction; 5, 5 minutes following induction; 6, 6 minutes following induction; 7, 7 minutes following induction; 8, 8 minutes following induction; 9, 9 minutes following induction; 10, 10 minutes following induction.

of involuntary myoclonic movements (MM) after induction of anesthesia is higher compared with propofol, though the incidence may vary from 0 to 70%.^{9,14,15} Myoclonus is caused by transient disinhibition of subcortical structures due to difference in cerebral blood flow. Another explanation is the difference of GABA-A receptor subunits within the central nervous system. The significant reduction of myoclonus occurs with drugs (benzodiazepines or opioids) and with pre-treatment with low dose etomidate, and propofol is known to inhibit the subcortical neuronal activity, or through enhancement of γ aminobutyric acid type A receptor.^{4,9,16,17} In this study by Doenicke et al. on EEG with etomidate, it was hypothesized that inhibitory circuits are depressed earlier and with low dose compared to excitatory circuits. This was the basis for using a low dose of etomidate as priming dose before induction with etomidate for reduction of myoclonus. They found that the myoclonus incidence decreased with 0.03 and 0.05 mg.kg⁻¹ priming with etomidate (i.e., low dose), and the incidence increased with 0.075 mg.kg⁻¹ priming dose (i.e., higher dose). Slow induction with etomidate 0.3 mg.kg⁻¹ by infusion over 90 seconds without pre-treatment reduced incidence of myoclonus to 28% compared to 84% with faster induction over 10 seconds in a study by Do et al.¹⁸

Etomidate and propofol are known to cause myoclonus though the incidence of myoclonus with propofol is very minimal (1:10,000). The mechanism for propofol-induced myoclonus was proposed to be subcortical disinhibition similar to etomidate.^{19,20} They also act on GABA-A receptors on excitatory and inhibitory neural circuit mechanisms. A recent study by Jinfeng et al. have shown a considerable decrease in the incidence of myoclonus with different doses of propofol following etomidate induction. There was decreasing incidence with increasing doses of propofol.⁵ Therefore, priming with low-dose propofol and etomidate were studied and compared along with fentanyl and midazolam to see its effectiveness in preventing myoclonus with etomidate induction.

The induction dose of etomidate is 0.3 mg.kg⁻¹ (0.2 to 0.6 mg.kg⁻¹). For an average 60kg adult, this will be around 18 mg. The loss of eyelash reflex and verbal commands were achieved with hardly 4.42 ± 2.12 mg dose of etomidate. The use of premedication and priming with propofol or etomidate has significantly reduced the induction dose of etomidate by more than 50%. Similar results were recorded in studies where priming was used in different doses and have shown a significant reduction in the induction dosage requirements of propofol.^{21,22} But etomidate induction dosage was not studied. Rather, a combination of etomidate-lipuro and propofol 1:1 (etofol) was found to be an effective induction regime with decreased dose requirement and decreased incidence of adverse reactions.²³

Etomidate has been the agent of choice for induction in view of hemodynamic stability.³ Next, etofol (1:1 admixture of etomidate-lipuro and propofol) was associated with best hemodynamic stability compared to etomidate and propofol group.²³ In this study by Saricaoglu et al., the 90 patients were randomly assigned to three groups in which induction was performed with etomidate-lipuro, propofol, or etomidate-lipuro-propofol admixture. The best hemodynamic stability with the least incidence of myoclonus and injection pain etofol group with least BIS value of 40 was observed. We could also get similar results with etomidate group as patients were hemodynamically stable. The group primed with etomidate and further induction with etomidate caused the least changes in hemodynamics. As the primed dose of propofol used was 1/10th of induction dose, least likely to cause hemodynamic instability. This property of hemodynamic stability would explain the response characteristics of ASA II patients in this study. As 5 patients of *p* primed group were ASA II and expected to be on a few disease control drugs, could lead to induction changes in hemodynamics. Though there were fluctuations but are not critical to cause compromise and all changes recovered back with intubation.

Limitations

There are some limitations to our study. Most of the studies have compared fentanyl and midazolam as counterparts for attenuation of myoclonus. Rather, we have used these drugs in both groups as a standard and routine practice. This is done especially to create a practical atmosphere for using these drugs to get their maximum beneficial effect. Even duration of myoclonus was not recorded.

Conclusion

Priming with etomidate and propofol are equally effective in reducing myoclonus with the added benefit of almost halving the induction dose of etomidate and hemodynamic stability.

Conflicts of interest

The authors declare no conflicts of interest.

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