Original Article

To compare the efficacy of three techniques in reducing etomidate-induced myoclonus - A randomised controlled trial

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ABSTRACT

Background and Aims: Etomidate is the preferred induction agent in haemodynamically unstable patients. Preventing etomidate-induced myoclonus (EIM) is important. The objective of this study was to compare the efficacy of three techniques of etomidate administration in preventing EIM. **Methods:** This randomised, controlled study included 296 patients. General anaesthesia (GA) was induced with etomidate as per the randomly allocated groups: control (C), priming (P), slow (S), and priming with slow injection (T). The incidence, time of onset, and grade of myoclonus were noted. The grade of pain on injection and the effect on various haemodynamic parameters were noted. The Kruskal-Wallis, Fisher's exact, and Chi-square tests were used for statistical analysis. $P < 0.05$ was considered to be statistically significant. **Results:** The study shows that the incidence of myoclonus was highest amongst Group C (73.0%), followed by Group P (52.7%), Group S (48.6%), and Group T (37.8%) ($P = 0.001$). Priming with a slow technique was most effective in preventing EIM and lowering the intensity of myoclonus. The incidence of grade 3 myoclonus was 5 (6.76%) in Group T when compared to 39 (52.7%) in Group C (mean difference [MD] =36.96, 95% CI: 7.45, 55.94; $P = 0.0001$). **Conclusion:** We observed that the priming and slow injection techniques were similar in reducing the incidence of EIM. However, the combination of priming and slow technique was the most effective.

Keywords: Anaesthesia, intravenous, etomidate, myoclonus, prevention, priming

INTRODUCTION

Etomidate is a popular intravenous (IV) anaesthetic induction agent due to its rapid onset of action and clearance, cardiostable with minimal respiratory side effects, marginal histamine release and cerebral protective effect.[1-4] However, adrenocortical suppression, myoclonus, and pain during IV administration are its adverse effects.[5] Myoclonus is defined as sudden, brief, involuntary muscle jerks (irregular or rhythmic), usually lasting for 10–50 ms.[6] Etomidate-induced myoclonus (EIM) may lead to serious complications such as raised intraocular pressure (IOP) and increased myocardial oxygen (O_2) consumption.[3,7] Hence, preventing EIM is important.

A large number of drugs have been studied for their ability to prevent these myoclonic movements.[1-3,7] However, these drugs may be associated with side effects such as respiratory depression. It is possible to eliminate the need for an additional drug, its inherent cost, and potential side effects by changing the technique of etomidate administration.[3,4,8]

To the best of our knowledge, no studies have compared the efficacy of priming dose technique,

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slow IV administration of induction dose technique, and a combination of priming dose with slow IV administration technique in preventing EIM. Therefore, we conducted this study to determine the efficacy of these techniques in reducing EIM, which is the primary objective. We also aimed to study the effectiveness of these methods on preventing pain with the IV administration of etomidate and its effect on haemodynamic parameters as our secondary objectives.

METHODS

This randomised, parallel-group, multiple-arm trial was conducted from January 2022 to December 2023 at a tertiary care hospital after approval from the Human Ethics Committee of Ramaiah Medical College, Bangalore (vide approval number MSRMC/EC/PG-64/01-2021, dated 28 January 2021). The study was registered with the Clinical Trials Registry-India (vide approval number CTRI/2021/03/032459, dated 31 March 2021, accessible at https://ctri.nic.in/Clinicaltrials/login.php). The study adhered to the principles of the Declaration of Helsinki (2013) and Good Clinical Practice guidelines. The manuscript was written as per the Consolidated Standards of Reporting Trials (CONSORT) guidelines. In this study, 296 patients aged 18–60 years with American Society of Anesthesiologists (ASA) physical status I and II posted for elective surgery under general anaesthesia (GA) were enroled. A written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. Patients with pre-existing adrenal disease, adrenocortical insufficiency, receiving or history of receiving steroids within the last 3 months, sepsis, seizure disorder, and hypersensitivity to etomidate were excluded from the study.

The study participants were randomly assigned into four groups of 74 patients each, using a computer-generated block randomisation list {International Business Machines Corporation (IBM Corp version 29.0.0.0 Armonk, New York)}: control (Group C), priming (Group P), slow administration (Group S), and priming with slow administration (Group T). Group allocation was concealed in sealed opaque envelopes and revealed to the independent anaesthesiologist before anaesthesia induction in the operation theatre (OT). The anaesthesia resident who prepared the drugs was not part of the study. Blinded assessors recorded pain on drug administration, haemodynamic parameters, and incidence and intensity of myoclonus. Due to varying drug administration speeds, the operator could not be blinded.

After the arrival of the patient in the operating room, a multi-parameter non-invasive monitor [CARESCAPE™ B650 (GE HealthCare, Chicago, Illinois, USA)] was attached, which included an electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximeter, and end-tidal carbon dioxide ($EtCO_2$). The baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were noted. A peripheral IV line (18 G) was secured, and Ringer's lactate infusion was started at 5 mL/kg/h. Pre-oxygenation was done with 100% O_2 for 3 minutes. GA was induced with IV etomidate [TROYMIDATE© (Troikaa Pharmaceuticals Limited, Ahmedabad, Gujarat, India). Each mL (of emulsion) contains etomidate 2 mg, soyabean oil IP, medium-chain triglycerides USP, glycerol IP, and egg lecithin] as per the randomly allocated- Group C: induction dose of IV 0.3 mg/kg etomidate, administered manually over 20 seconds; Group P: priming dose of IV 0.03 mg/kg etomidate, followed after 1 minute by an induction dose of IV 0.3 mg/kg, administered over 20 seconds; Group S: induction dose of IV 0.3 mg/kg etomidate, slowly administered over 2 minutes with a syringe pump; Group T: A priming dose of IV 0.03 mg/kg etomidate is followed after 1 minute by an induction dose of 0.3 mg/kg, slowly administered over 2 minutes with a syringe pump.

All patients were observed for 3 minutes from the start of administration of induction dose of IV etomidate for occurrence of myoclonus. The intensity of myoclonic movement was graded as: 0 - no myoclonus; 1 - mild myoclonus (short movement of a body segment, e.g. a finger/wrist); 2 - moderate myoclonus (mild movement of two different muscle groups, e.g. face and arm); 3 - severe myoclonus (intense myoclonic movement in two or more muscle groups/fast limb adduction).[8] Pain on IV etomidate administration was assessed after a full dose of etomidate was given, based on a four-grade pain scale: 0 - no pain; 1 - mild (pain reported only when asked); 2 - moderate (pain reported without being asked/reported when asked with associated behavioural symptoms); 3 - severe (verbal response, grimacing, pulling the arm, tearing eye).[9] At 3 minutes following the onset of induction, all patients were given IV fentanyl 2 μg/kg and IV atracurium 0.5 mg/kg to aid tracheal intubation. Tracheal intubation was done 3 minutes following IV atracurium and

confirmed by auscultation and $EtCO_2$. Anaesthesia maintenance was done with isoflurane minimum alveolar concentration (MAC) 1–1.2 in response to haemodynamic variation, a 50:50 air oxygen mixture, and intermittent positive pressure ventilation. After the surgery was completed, residual neuromuscular blockade was reversed with IV neostigmine and glycopyrrolate, and the trachea was extubated.

The primary outcome of varying incidences of myoclonus amongst the four study groups was observed for 3 minutes from the start of administration of the induction dose of IV etomidate. We also recorded the intensity and time of onset of myoclonus. The secondary outcomes of pain on IV etomidate administration and the effect on haemodynamic parameters were compared across the groups from the beginning of induction to 5 minutes after tracheal intubation. Adverse effects such as increased oral secretions and postoperative nausea and vomiting (PONV) up to 1 hour after extubation were also noted as a secondary outcome.

The sample size was calculated based on a study by Parul Mullick *et al*.[4] The incidence of EIM was significantly lower in the priming group (60.3%, 95% confidence interval [CI]: 48.0, 71.5; $P = 0.001$) than in control (84.1%, 95% CI: 72.9, 91.3; $P = 0.003$) and slow administration group (77.8%, 95% CI: 66.0, 86.4; $P = 0.034$). In the absence of studies providing the incidence in Group T (priming with slow administration group) of this study, it was assumed that the incidence of myoclonus may be lesser in Group T. Based on the above findings, with a power of 80% and an alpha error of 5%, it was estimated that at least 74 patients need to be included in each group of this study.

The data were organised and analysed in Microsoft Excel, followed by an in-depth analysis utilising Statistical Package for the Social Sciences (SPSS) statistics software version 26.0 (International Business Machines Corporation (IBM Corp), Armonk, NY, USA). Categorical variables (myoclonus incidence) were displayed as frequency and percentage. Continuous variables (myoclonus intensity) were reported as mean [standard deviation (SD)]. P value <0.05 was deemed statistically significant, indicating a non-chance difference between the groups. The Kruskal-Wallis test assessed the statistical significance of differences between groups for continuous variables (age, weight, and time of onset of myoclonus). The Chi-square and Fisher's exact tests were utilised to evaluate the significance of relationships amongst categorical variables (gender, intensity of myoclonus, and pain on drug administration).

RESULTS

In total, 350 patients were assessed for eligibility to be included in the study, and 296 patients were enroled in the study [Figure 1]. The demographic parameters were comparable across the study groups.

The overall incidence of myoclonus was 53% (95% CI: 31.40, 55.94), amongst the study participants. The study shows that the incidence of myoclonus [Table 1] was highest amongst Group C (72%, 95% CI: 32.48, 58.63), followed by Group P (52%, 95% CI: 19.44, 40.83), Group S (48%, 95% CI: 9.55, 20.37), and Group T (37%, 95% CI: 5.51, 14.24). The incidence of myoclonus amongst the four groups was statistically significant ($P = 0.001$). Although the incidence of myoclonus was lower in Group T, there was no statistical significance between groups T and P (MD:

Table 1: Showing incidence, intensity, time of onset of myoclonus, and pain on injection amongst the four groups

Variables	Group C (*n*=74)	Group P (*n*=74)	Group S (*n*=74)	Group T (*n*=74)	Total	*P*
Incidence of myoclonus	54	39	36	28	157	0.0005
Intensity of myoclonus						
0	20	35	38	44	137	<0.0001
1	2	5	4	8	19	
2	13	19	16	15	63	
3	39	15	16	5	75	
Time of onset of myoclonus (s)	38.34 (32.74) (30.75, 45.92)	36.27 (47.35) (25.30, 47.24)	33.80 (45.05) (23.36, 44.23)	32.39 (44.25) (21.99, 42.79)	-	0.001
Pain on injection						
0	70	71	74	71	286	-
1	1	3	0	3	7	
2	3	0	0	0	3	
3	0	0	0	0	0	

Data presented as mean (standard deviation) (95% confidence interval) or number of patients

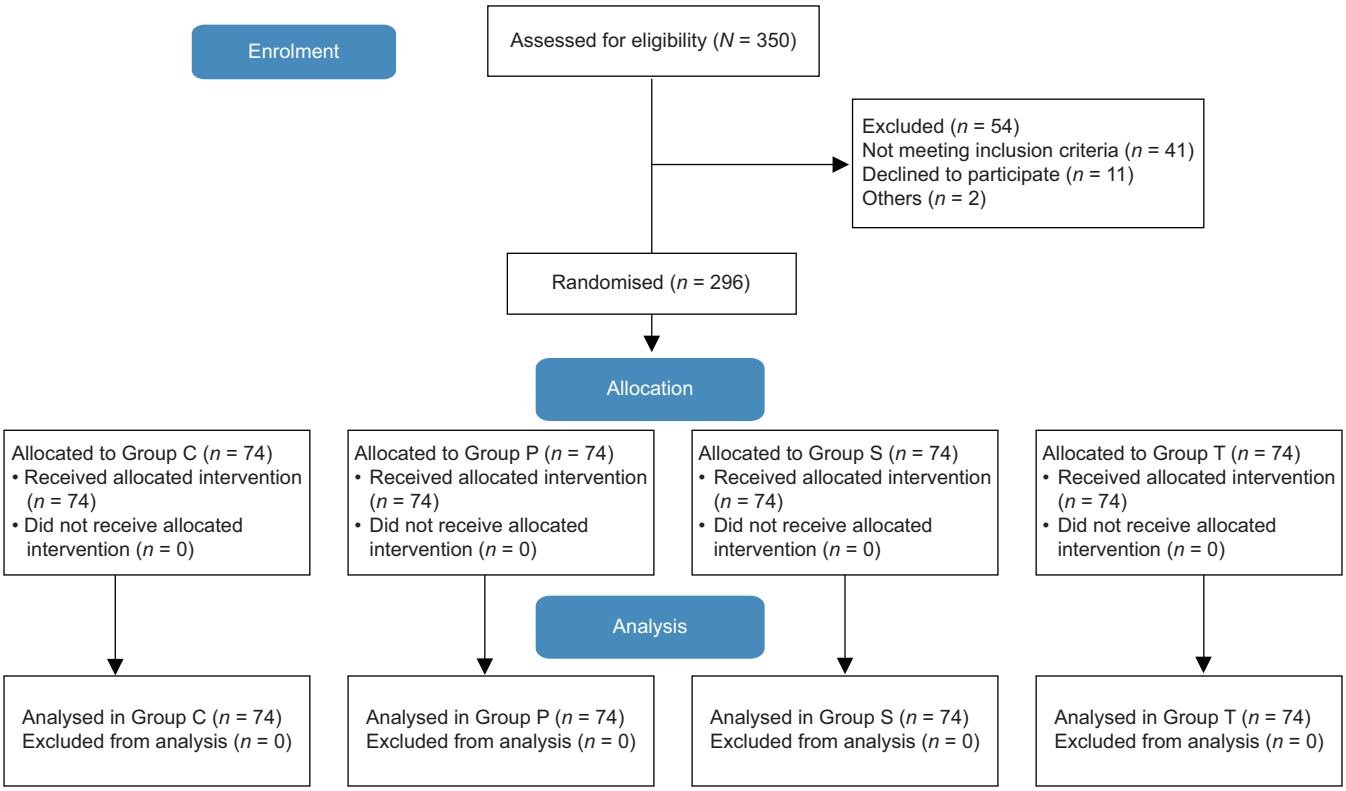

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram for patient recruitment

30.28, 95% CI: 5.29, 54.81, $P = 0.069$) or groups T and S (MD: 5.28, 95% CI: 12.30, 22.30, $P = 0.1843$).

The intensity of myoclonus showed a significant distribution, with 47% having no symptoms and 26% experiencing severe myoclonus ($P = 0.0001$) [Table 1]. Severe myoclonus was mostly experienced by patients of Group C. The inter-group comparison revealed a significant difference in the intensity of myoclonus between Group C and Group P (MD: 0.77, 95% CI: 0.186, 1.355, $P = 0.0001$), Group C and Group S (MD: 0.82, 95% CI: 0.23, 1.41, $P = 0.001$), Group C and Group T (MD: 1.22, 95% CI: 0.68, 1.76, $P = 0.0001$), Group T and Group S (MD: −0.40, 95% CI: −0.93, 0.13. $P = 0.048$). Groups P and S had no significant difference in the intensity of myoclonus (MD: 0.054, 95% CI: −0.52, 0.63, $P = 0.913$). Although Group P had a higher incidence of grade 3 myoclonus, there was no significance between groups P and T (MD: 0.45, 95% CI: 0.06, 0.98, $P = 0.053$).

The study showed that the time of onset of myoclonus was slowest in Group T and fastest in Group C. The difference was statistically significant (MD: 5.95, 95% CI: 25.35, 45.045, $P = 0.001$) [Table 1].

Most (96.6%) of the patients had no pain on IV administration, 2.3% had a pain score of 1, and 1% had a score of 2. None of the patients had a pain score of 3 [Table 1].

The study revealed that the mean HR between the four groups at 1-minute post-induction [$P = 0.008$, 79.6 (SD: 12.5), 95% CI: 76.7, 82.5] and 2 minutes after intubation ($P = 0.01$, 77.2 (SD: 11.7), 95% CI: 74.4, 79.9) were statistically significant. The study showed that HR, MAP, and SpO_2 were not statistically significant at any time point [Figures 2–4].

The incidence of PONV ($P = 0.864$) and increased oral secretions did not differ significantly amongst the groups.

DISCUSSION

This randomised controlled trial yielded evidence that a synergistic approach, combining priming and slow IV administration techniques, offers the most effective strategy for mitigating the incidence of EIM. Priming and slow IV administration techniques demonstrated significant reductions in EIM when employed individually.

The prevalence of EIM is around 80% in non-premedicated patients. Preventing EIM is

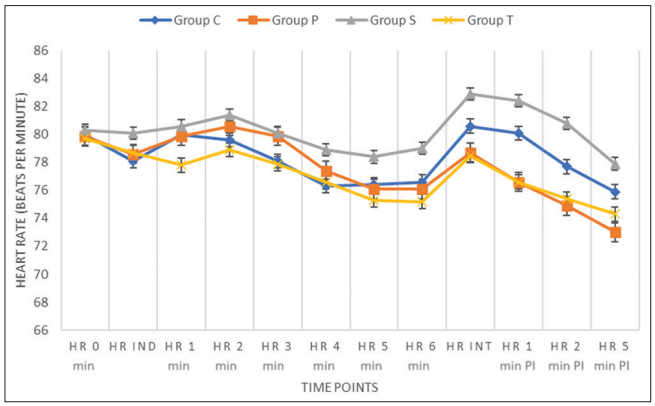

Figure 2: A line diagram showing intraoperative trends of heart rate. HR = Heart Rate, min = minutes, IND = Induction, INT = Intubation, PI = Post Intubation

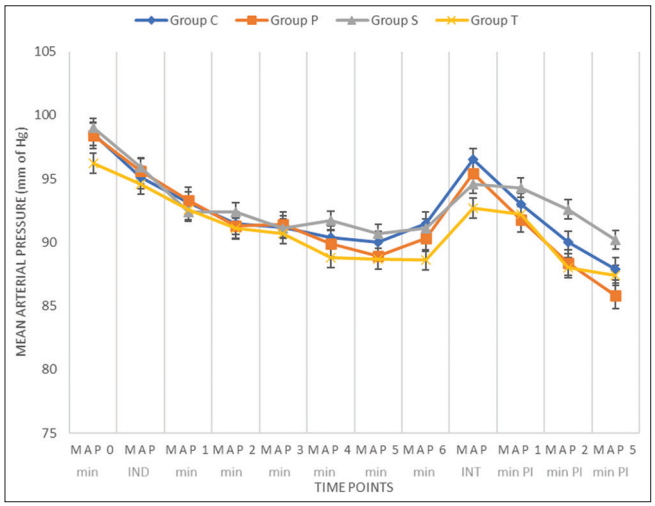

Figure 3: A line diagram showing intraoperative trends of mean arterial pressure. MAP = Mean Arterial Pressure, min = minutes, IND = Induction, INT = Intubation, PI = Post Intubation

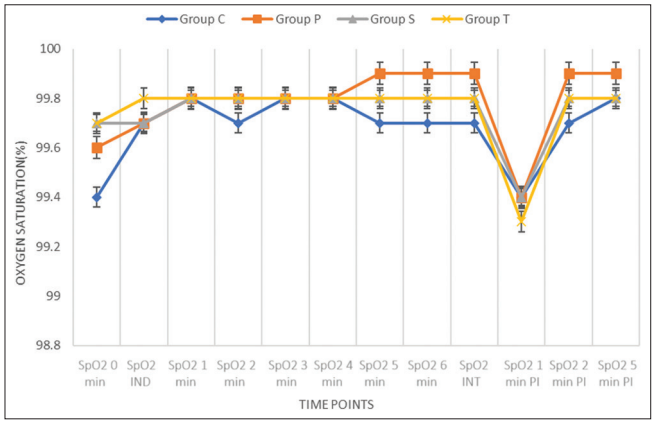

Figure 4: A line diagram showing intraoperative trends of oxygen saturation. SpO2 = Oxygen saturation, min = minutes, IND = Induction, INT = Intubation, PI = Post Intubation

important as it can lead to adverse events such as raised IOP, Mendelson syndrome, and difficult mask ventilation.[10] Various studies have been conducted to test the efficacy of different drugs (benzodiazepines, opiates, and alpha agonists) and techniques of injection to prevent EIM.[1,3,4,7-9,11-14] However, they are associated with side effects such as apnoea, cognitive dysfunction, hypotension, and an increased cost due to the additional drug.[3,9,14,15] Premedication with low-dose etomidate is more effective in preventing EIM.[3]

Our results were consistent with those published by S H Do *et al*.,[8] who found that the incidence of EIM was significantly lower in the slow injection group compared to the fast injection group. Similar results were seen in a study done by Parul Mullick *et al*.,[4] whose study revealed that priming with 0.03 mg/kg of etomidate was significantly better than slow injection in reducing the incidence and intensity of EIM. Research carried out by Sedighinejad *et al*.,[3] Aissaoui *et al*.,[11] Doenicke *et al*.,[12] and Holdcroft *et al*.[13] have established that priming reduced the incidence and intensity of myoclonus. Do *et al*.[8] found that even slow injection of etomidate significantly reduced the intensity of EIM. However, in our study, priming and slow injection had similar efficacy in preventing EIM, but it was not statistically significant. We also noted that Group T had delayed onset of myoclonus. The delayed onset could be due to synchronised depression of cortical and subcortical activity.[4]

It is hypothesised that subcortical disinhibition is the cause of EIM. Studies have shown that opiates and benzodiazepines prevent subcortical disinhibition.[12,16,17] Kugler *et al*.[18] suggested that compared to excitatory neuronal circuits, inhibitory neuronal circuits are depressed earlier, even by lower doses of etomidate. Based on this hypothesis, Doenicke *et al*.[12] proposed that this excitatory myoclonus is caused by nonequilibrium of etomidate at different sites of the central nervous system (CNS). Differences in cortical and subcortical blood flow cause temporary fluctuations, leading to cortical inhibition and eventual suppression of both inhibitory and excitatory circuits. Pre-treatment, priming and slow injection reduce this disequilibrium, preventing subcortical disinhibition.[4,12] No studies have examined the effect of priming with slow injection.

Pain on IV administration was seen in the older propylene glycol preparation due to high osmotic pressure.[19,20] The new lipid-emulsion preparation has a lesser incidence of pain on injection, which is

congruent with our results.[20,21] The control group had the highest incidence of pain due to the fast rate of IV administration.

Etomidate is known for its cardio-stable nature, which is attributed to negligible dose-dependent effect on the sympathetic nervous system and baroreceptors. It is the induction agent of choice in patients with compromised cardiac function.[22-28] Haemodynamic parameters were comparable across our study groups.

Etomidate is known to cause PONV and increased oral secretions during myoclonus, which was negligible in our study. Our results were consistent with a study by St Pierre *et al*.,[29] which found that etomidate does not increase the incidence of PONV.

The present study had limitations: operator blinding could not be done due to varying injection speeds across the groups. Neuromuscular blockade can mask delayed myoclonic movements. Intraoperative EEG monitoring could have determined true EIM incidence. Postoperative creatinine phosphokinase could have been measured to assess muscle damage.

CONCLUSION

We observed that the priming and slow injection techniques were similar in reducing the incidence of EIM. However, the combination of priming and slow technique was the most effective.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

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Conflicts of interest

There are no conflicts of interest.

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