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COMPARATIVE ASSESSMENT OF THE EFFICACY OF TECHNIQUES FOR ADMINISTERING ETOMIDATE IN PREVENTION OF ETOMIDATE INDUCED MYOCLONUS.

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Abstract

Background: Etomidate is a preferred induction agent in patients with limited cardiovascular reserve but is frequently associated with etomidate-induced myoclonus (EIM), which can be distressing and potentially hazardous in selected clinical scenarios. Various pharmacological and technique-based strategies have been proposed to attenuate EIM, but the optimal practical approach in routine practice remains unclear.

Methods: In this prospective, randomized, observational study, 60 ASA I–II patients aged 18–60 years scheduled for elective surgery under general anesthesia were allocated into three groups (n=20 each): Control (normal saline pretreatment, etomidate 0.3 mg/kg rapid bolus), Priming + Slow Injection (priming dose etomidate 0.03 mg/kg followed 60 seconds later by 0.27 mg/kg over 30–60 seconds), and Fentanyl Pretreatment (fentanyl 2 µg/kg pretreatment, etomidate 0.3 mg/kg rapid bolus). Incidence and severity of myoclonus (4-point scale) were the primary outcomes; onset, duration of myoclonus, time to loss of consciousness, hemodynamics, pain on injection, and adverse effects were recorded as secondary outcomes.

Results: Baseline demographic and clinical characteristics were comparable across groups. The incidence of EIM was significantly lower in the Priming + Slow Injection (30%) and Fentanyl Pretreatment (40%) groups compared with the Control group (85%, $p<0.001$). Severe (Grade 3) myoclonus occurred in 25% of control patients but was completely abolished in both intervention groups. Among patients who developed myoclonus, onset was significantly delayed and duration significantly shortened in the Priming + Slow Injection group (52.8±8.3 s and 8.2±2.5 s, respectively) compared with Fentanyl Pretreatment (38.5±6.7 s; 10.8±3.2 s) and Control (24.3±5.2 s; 18.5±4.8 s; $p<0.001$). Hemodynamic variables remained stable and comparable between groups, pain on injection was minimal, and adverse events were infrequent with no significant inter-group differences.

Conclusion: Both priming with slow injection of etomidate and fentanyl pretreatment effectively reduce the incidence and severity of etomidate-induced myoclonus without compromising hemodynamic stability or increasing adverse effects. The priming with slow injection technique offers superior control of onset and duration of myoclonus and represents a simple, drug-sparing strategy suitable for routine clinical practice.

Keywords: etomidate-induced myoclonus; priming dose; slow injection; fentanyl pretreatment; anesthetic induction**.**

Introduction- Etomidate is a widely used intravenous induction agent because it provides rapid hypnosis with relatively stable haemodynamics, making it attractive in patients with limited cardiovascular reserve. However, etomidate-induced myoclonus (EIM)—involuntary, brief skeletal muscle jerks occurring around induction—remains a frequent and clinically relevant adverse effect, reported in unpremedicated patients at rates as high as 50%–80%. These movements are not only distressing and can interfere with monitoring, but may also be hazardous in selected clinical situations such as non-fasted patients (risk of regurgitation/aspiration) and those with open-globe injuries where abrupt increases in intraocular pressure can be detrimental.[1]

The pathophysiology of EIM is not fully established; a commonly accepted explanation is transient disequilibrium between cortical and subcortical neuronal suppression during early etomidate effect, leading to "disinhibition" and myoclonic activity.[2] Because the mechanism is multifactorial and patient susceptibility varies, multiple strategies have been explored to reduce both incidence and severity of EIM, including (a) modification of the **technique** of etomidate administration and (b) pharmacological pretreatment/co-induction.

Among technique-based methods, etomidate "priming" involves administering a small sub-hypnotic dose before the full induction dose to attenuate the abrupt neurophysiologic transition thought to precipitate myoclonus. A prospective randomized double-blind study using an etomidate priming dose of 0.03 mg/kg given 60 seconds before induction demonstrated a marked reduction in myoclonus compared with placebo.[3] Another randomized controlled trial comparing priming versus slow injection found priming to be more effective than slow injection in reducing the incidence of EIM, while effects on severity were comparable between these two approaches.[2] Technique modification is appealing because it may reduce the need for additional drugs and their potential adverse effects, an important consideration in day-care anesthesia and in patients at risk of respiratory depression or haemodynamic instability.

Pharmacological prevention has focused on agents that modulate inhibitory neurotransmission or blunt subcortical activity, including opioids and benzodiazepines. In a large prospective randomized double-blind study, pretreatment with a combination of fentanyl (2 μg/kg) and midazolam (0.03 mg/kg) administered before etomidate significantly reduced both incidence and moderate-to-severe grades of myoclonus compared with fentanyl alone or midazolam alone.[1] This suggests that combining drugs acting through different receptor systems may provide additive or synergistic protection against EIM, although such regimens must be balanced against risks like apnea or excessive sedation.

In parallel, other non-opioid options such as magnesium have been studied to reduce EIM, with the rationale of modulating excitatory pathways and avoiding respiratory depression associated with opioids/benzodiazepines.[4] Overall, the available evidence supports a comparative assessment of three practical preventive approaches—priming dose technique, slow injection technique, and pharmacologic pretreatment (single drug or combination)—to identify the method that best reduces EIM while preserving etomidate's haemodynamic advantages and minimizing adverse effects.

Methodology

Study Design and Setting

This prospective, randomized, observational study was conducted in the Department of Anesthesiology at Tertiary care center written informed consent from all participants.

Sample Size Calculation

The sample size was calculated based on a pilot study showing myoclonus incidence of 80% in the control group and an expected reduction to 30% in the intervention groups. Using a power of 80%

and alpha error of 0.05, a minimum of 18 patients per group were required. Accounting for potential dropouts, 20 patients were enrolled in each group, totaling 60 patients.

Study Population

Inclusion Criteria:

- Patients aged 18-60 years
- ASA physical status I or II
- Scheduled for elective surgery under general anesthesia
- Body Mass Index 18-30 kg/m²

Exclusion Criteria:

- Known allergy to etomidate, fentanyl, or any study drugs
- History of seizure disorders or movement disorders
- Psychiatric illness or medications affecting muscle tone
- Pregnancy or lactation
- Cardiovascular, hepatic, or renal dysfunction
- Recent use of opioids or sedatives within 24 hours
- Difficult airway anticipated
- Patient refusal

Patients were randomly divided into three groups of 20 each using computer-generated random numbers placed in sealed opaque envelopes. The groups were: Group C (Control), Group PS (Priming with Slow Injection), and Group F (Fentanyl Pretreatment). An anesthesiologist not involved in patient assessment prepared the study drugs, ensuring double-blinding. The anesthesiologist administering the drugs and the observer recording outcomes were blinded to group allocation.

Preoperative Preparation

All patients underwent thorough preoperative evaluation including history, physical examination, and relevant investigations. Patients were kept nil per oral for 8 hours for solids and 2 hours for clear fluids. No premedication was administered. On arrival to the operating room, standard monitoring was established including electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), and capnography.

Anesthetic Technique

After establishing intravenous access with 18G cannula, patients were preloaded with Ringer's lactate solution. Baseline vital parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and SpO_2) were recorded. All patients received injection glycopyrrolate 0.004 mg/kg intravenously 5 minutes before induction. Preoxygenation was performed with 100% oxygen for 3 minutes.

Group C (Control): Patients received 5 ml normal saline as pretreatment 2 minutes before induction, followed by etomidate 0.3 mg/kg as rapid bolus injection over 5 seconds.

Group PS (Priming with Slow Injection): Patients received 5 ml normal saline as pretreatment 2 minutes before induction, followed by priming dose of etomidate (10% of total calculated dose = 0.03 mg/kg) given over 5 seconds. After 60 seconds, the remaining etomidate dose (0.27 mg/kg) was administered slowly over 30-60 seconds.

Group F (Fentanyl Pretreatment): Patients received injection fentanyl 2 µg/kg diluted in 5 ml normal saline as pretreatment 2 minutes before induction, followed by etomidate 0.3 mg/kg as rapid bolus injection over 5 seconds.

Following loss of consciousness, all patients received injection succinylcholine 1.5 mg/kg for tracheal intubation. Anesthesia was maintained with oxygen, nitrous oxide, isoflurane, and vecuronium bromide as per standard protocol.

Outcome Measurements

Primary Outcome:

- Incidence and severity of myoclonus assessed from etomidate injection until intubation

Myoclonus Grading Scale:

- Grade 0: No myoclonus
- Grade 1: Mild myoclonus (minor movement in face, neck, or one extremity)
- Grade 2: Moderate myoclonus (movement involving trunk or more than one extremity)
- Grade 3: Severe myoclonus (vigorous movement involving trunk and extremities or fast adduction of limbs)

Secondary Outcomes:

- Onset time of myoclonus (time from etomidate injection to first myoclonic movement)
- Duration of myoclonus (time from onset to cessation of myoclonic movements)
- Time to loss of consciousness (time from etomidate injection to loss of eyelash reflex)
- Pain on injection assessed on 4-point scale (0=none, 1=mild, 2=moderate, 3=severe)
- Hemodynamic parameters (heart rate, blood pressure) recorded at baseline, post-induction, 1 minute post-intubation, and 5 minutes post-intubation
- Adverse effects including nausea, vomiting, respiratory depression, bradycardia, or allergic reactions

A single trained anesthesiologist, blinded to group allocation, observed and recorded all myoclonic movements and their characteristics.

Results

A total of 60 patients were enrolled and randomly allocated into three groups of 20 patients each, with all groups being comparable in terms of baseline demographic and clinical characteristics including age, gender, weight, height, BMI, ASA physical status, and duration of surgery (Table 1). The incidence of etomidate-induced myoclonus was significantly lower in the priming with slow injection group (30%) and fentanyl pretreatment group (40%) compared to the control group (85%), with $p<0.001$ (Table 2). Severe myoclonus (Grade 3) was completely eliminated in both intervention groups, while the control group had 5 patients (25%) experiencing severe myoclonus. Hemodynamic parameters including heart rate, systolic blood pressure, and diastolic blood pressure remained stable across all three groups at baseline, post-induction, 1 minute post-intubation, and 5 minutes post-intubation, with no statistically significant differences observed ($p>0.05$) (Table 3). Among patients who developed myoclonus, the priming with slow injection group demonstrated significantly prolonged onset time (52.8±8.3 seconds) compared to fentanyl pretreatment (38.5±6.7 seconds) and control groups (24.3±5.2 seconds), with correspondingly reduced duration of myoclonus (8.2±2.5 seconds vs 10.8±3.2 seconds vs 18.5±4.8 seconds respectively, $p<0.001$) (Table 4). Pain on injection was minimal across all groups with 90-95% of patients reporting no pain, and adverse effects including nausea, vomiting, respiratory depression, and bradycardia occurred infrequently with no significant inter-group differences ($p>0.05$) (Table 5).

Table 1: Demographic and Baseline Characteristics

Parameter	Control Group (n=20)	Priming + Slow Injection (n=20)	Fentanyl Pretreatment (n=20)	p-value
Age (years)	40.5 ± 12.3	38.8 ± 10.7	41.2 ± 11.5	0.78
Gender (M/F)	12/8	11/9	13/7	0.85
Weight (kg)	64.2 ± 8.5	65.8 ± 9.2	63.5 ± 8.9	0.67
Height (cm)	165.3 ± 6.8	166.5 ± 7.2	164.8 ± 6.5	0.72
BMI (kg/m²)	23.5 ± 2.8	23.9 ± 3.1	23.3 ± 2.6	0.81
ASA Grade (I/II)	14/6	15/5	13/7	0.76
Duration of surgery (min)	78.5 ± 22.4	82.3 ± 25.1	75.8 ± 20.6	0.58

Table 2: Incidence and Severity of Etomidate-Induced Myoclonus

Myoclonus Grade	Control (n=20)	Priming + Slow Injection (n=20)	Fentanyl Pretreatment (n=20)	p-value
Grade 0 (None)	3 (15%)	14 (70%)*	12 (60%)*	<0.001
Grade 1 (Mild: minor movement in face/neck)	4 (20%)	4 (20%)	5 (25%)	0.87
Grade 2 (Moderate: movement in trunk/limbs)	8 (40%)	2 (10%)*	3 (15%)*	0.02
Grade 3 (Severe: vigorous movement, >1 group)	5 (25%)	0 (0%)*	0 (0%)*	<0.01
Total Incidence	17 (85%)	6 (30%)*	8 (40%)*	<0.001

*Statistically significant compared to control group

Table 3: Hemodynamic Parameters at Different Time Points

Parameter	Time Point	Control (n=20)	Priming + Slow Injection (n=20)	Fentanyl Pretreatment (n=20)	p-value
Heart Rate (bpm)	Baseline	82.5 ± 10.2	81.3 ± 9.8	83.2 ± 10.5	0.82
	Post-induction	78.8 ± 9.5	77.2 ± 8.9	76.5 ± 9.2	0.68
	1 min post-intubation	88.5 ± 11.3	87.2 ± 10.8	86.8 ± 11.1	0.89
	5 min post-intubation	80.3 ± 9.7	79.5 ± 9.3	81.2 ± 10.1	0.85
SBP (mmHg)	Baseline	128.5 ± 14.2	126.8 ± 13.5	129.3 ± 14.8	0.79
	Post-induction	118.2 ± 12.5	116.5 ± 11.8	117.8 ± 12.3	0.88
	1 min post-intubation	135.8 ± 15.2	134.2 ± 14.5	136.5 ± 15.8	0.83
	5 min post-intubation	122.5 ± 13.2	121.8 ± 12.6	123.2 ± 13.5	0.92
DBP (mmHg)	Baseline	78.3 ± 8.5	77.5 ± 8.2	79.2 ± 8.8	0.76
	Post-induction	72.5 ± 7.8	71.8 ± 7.5	73.2 ± 8.1	0.81
	1 min post-intubation	84.2 ± 9.2	83.5 ± 8.8	85.1 ± 9.5	0.87
	5 min post-intubation	76.8 ± 8.3	76.2 ± 8.0	77.5 ± 8.5	0.89

Table 4: Onset Time and Duration of Myoclonus

Parameter	Control (n=17)†	Priming + Slow Injection (n=6)†	Fentanyl Pretreatment (n=8)†	p-value
Onset time (seconds)	24.3 ± 5.2	52.8 ± 8.3*	38.5 ± 6.7*	<0.001
Duration (seconds)	18.5 ± 4.8	8.2 ± 2.5*	10.8 ± 3.2*	<0.001
Time to loss of consciousness (seconds)	32.8 ± 6.5	62.5 ± 9.2*	45.3 ± 7.8*	<0.001

†Only patients who developed myoclonus; *Statistically significant compared to control ($p<0.05$)

Table 5: Pain on Injection and Adverse Effects

Parameter	Control (n=20)	Priming + Slow Injection (n=20)	Fentanyl Pretreatment (n=20)	p-value
Pain on Injection				
Grade 0 (None)	19 (95%)	19 (95%)	18 (90%)	0.68
Grade 1 (Mild)	1 (5%)	1 (5%)	2 (10%)	0.68
Grade 2 (Moderate)	0 (0%)	0 (0%)	0 (0%)	-
Grade 3 (Severe)	0 (0%)	0 (0%)	0 (0%)	-
Other Adverse Effects				
Nausea	2 (10%)	1 (5%)	2 (10%)	0.72
Vomiting	1 (5%)	0 (0%)	1 (5%)	0.58
Respiratory depression	0 (0%)	0 (0%)	1 (5%)	0.36
Bradycardia	0 (0%)	0 (0%)	2 (10%)	0.12

Discussion- The results of this study highlight the effectiveness of two interventions—priming with slow injection and fentanyl pretreatment—on reducing the incidence and severity of etomidate-induced myoclonus compared to a control group. A total of 60 patients were randomized into three groups, and baseline demographic and clinical characteristics were comparable across all groups. The primary finding was that both interventions significantly reduced the incidence of myoclonus, with the priming with slow injection group showing the most pronounced effect (30%), followed by the fentanyl pretreatment group (40%), compared to 85% in the control group, which is consistent with Isitemiz et al. [5] who reported identical rates of 40% with fentanyl pretreatment and 85% in control groups, validating the reproducibility of these findings across different populations. Our combined priming with slow injection approach achieved superior results (30%) compared to Mullick et al. [2] who reported 60.3% incidence with priming alone and 77.8% with slow injection alone, suggesting that combining these techniques provides additive benefits beyond either technique used independently. These findings were further supported by Do et al. [6] who demonstrated that slow injection over 2 minutes reduced myoclonus to 28%, similar to our combined approach.

In terms of severity, both interventions were notably effective in eliminating severe (Grade 3) myoclonus, which was observed in 25% of patients in the control group but was absent in both intervention groups, which aligns with Zhou et al. [7] meta-analysis showing that pretreatment strategies reduced severe myoclonus with a relative risk of 0.12. Additionally, the onset time and duration of myoclonus were significantly prolonged and reduced, respectively, in the intervention groups, with the priming with slow injection group exhibiting the longest onset time (52.8±8.3 seconds) and the shortest duration (8.2±2.5 seconds), comparable to Do et al.[6] who observed time to loss of consciousness of 106±22 seconds with slow injection technique.

Hemodynamic parameters, including heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), remained stable across all groups throughout the study, with no significant

differences observed between the groups. This suggests that the interventions did not have any major hemodynamic side effects and were well tolerated by patients, consistent with Luan et al. [8] who demonstrated that pharmacological pretreatment with dexmedetomidine maintained hemodynamic stability while reducing myoclonus.
Furthermore, pain on injection was minimal across all groups, with the vast majority of patients (90-95%) reporting no pain, and adverse effects such as nausea, vomiting, respiratory depression, and bradycardia were infrequent with no significant differences between groups, similar to the findings of Isitemiz et al. [5] who reported no respiratory depression with fentanyl pretreatment at the doses used. These findings underscore the safety of the interventions in addition to their efficacy in reducing myoclonus.

Conclusion- in our study both priming with slow injection and fentanyl pretreatment are effective strategies for reducing the incidence and severity of etomidate-induced myoclonus without significantly impacting hemodynamics or causing major adverse effects. The priming with slow injection group demonstrated superior results in terms of onset time and duration of myoclonus, while both interventions proved to be safe and well tolerated.

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