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EFFECT OF PRIMING IN PREVENTING MYOCLONIC MOVEMENTS AFTER INTRAVENOUS INDUCTION WITH ETOMIDATE IN ADULT PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROLLED INTERVENTIONAL STUDY

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ABSTRACT
Etomidate is a hypnotic drug used as an intravenous anaesthetic induction agent. Etomidate causes myoclonic movements in 50-80% patients after induction which makes it less desirable for induction. Aim: Present study was to determine the effect of priming in preventing myoclonic movements after intravenous injection with etomidate in adult patients undergoing cardiac surgery. Materials and Methods: 108 patients ASA grade III scheduled for elective cardiac surgery were allocated randomly in two groups- Group A (n=54): Patients received induction dose of 0.3mg/kg I.V. etomidate, Group B (n=54): Patients received a priming dose of 0.03mg/kg etomidate I.V. followed after 1 minute by induction dose of 0.3 mg/kg I.V. etomidate over 20 seconds. 3 minutes after the start of induction with etomidate, patients in both groups were given injection fentanyl 4mcg/kg followed by injection Rocuronium (1mg/kg bodyweight) to facilitate tracheal intubation. The occurrence and intensity of myoclonus were observed for 3 min from the start of injection of the induction dose and graded clinically by a blinded observer as: 0=no myoclonus, 1=mild myoclonus, 2=moderate myoclonus and 3=severe myoclonus. Result: The average dose of etomidate used during induction and demographic variables were similar in both the groups. The incidence of myoclonus in priming Group (27/54 [50%] was significantly lower than in control Group (45/54 [83.33%].Myoclonus of moderate or severe grade occurred in significantly more patients in control Group (68.3%) than in priming Group (36.5%).Conclusion: Pre-treatment with etomidate (0.03 mg/kg), given 60 seconds before induction of anaesthesia is more effective in reducing the incidence of etomidate-induced myoclonus without related side-effects.

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INTRODUCTION

Etomidate is a non-barbiturate hypnotic drug derived from a carboxylated imidazole and widely used as an intravenous anaesthetic induction agent [1]. Hypnotic action is through GABA A receptors facilitation. It has rapid onset of action and stable haemodynamic profile with minimal effects on respiratory system as compared with other induction agents. Being a cardio-stable drug, it is especially preferred in patients who are haemodynamically unstable [2]. However Etomidate has several adverse effects including Pain at the injection site, Post-operative nausea/vomiting, Electroencephalography (EEG) activation, Adrenal suppression, and Myoclonus [3]. The incidence of myoclonus has been reported as much as 50-80% after Etomidate induction [4]. Myoclonus can increase the risk of regurgitation and aspiration in patients with full stomach also increases intraocular pressure, so it may cause vitreous prolapse in patients with open eye injuries [5]. Altering the speed of injection of Etomidate and pre-treatment with drugs such as Lidocaine, Midazolam, Magnesium, Fentanyl and Dexmedetomidine have been investigated as ways of reducing Etomidate Induced Myoclonus (EIM) with variable results. Pre-treatment with a low dose of Etomidate (Priming dose) can itself reduce the incidence of EIM, eliminating the need for an additional drug with its inherent cost and potential side effects [6]. With this background, the present study was conducted to observe the effect of priming in preventing myoclonic movements after intravenous induction with etomidate in adult patients undergoing cardiac surgery under general anaesthesia.

MATERIALS AND METHODS

This Hospital based Prospective Randomized Controlled Interventional Study was conducted in a Tertiary Care Hospital with due permission from Institutional Ethics Committee and Research Review Board till the desired sample size was completed.

In this study 108 patients aged between 20 to 60 years, Scheduled for Cardiac surgery were included. Patients were randomly allocated into two groups of 54 patients each, using a Computerized Random Number Table.

Patients with pre-existing Adrenal disease or Adrenocortical insufficiency, History of receiving steroids within last3 months, History of seizures, History of allergy to the study drug, Anticipated Difficult Airway and Psychiatric disorders were excluded from this study. A sample size of 54 cases in each group were required at 95% confidence and 80% power to verify the expected difference of 24% in occurrence of myoclonus. All the patients under study were subjected to detailed pre-anaesthetic evaluation which included detailed history taking, physical examination and airway assessment. Written informed consent was obtained from all patients after explaining about the study purpose, advantages and risks of procedure.

On arrival in Operation Theatre fasting status was confirmed. Routine monitoring like ECG and SpO2 were attached and peripheral I.V. line was taken. Femoral artery cannulation was done for invasive arterial pressure monitoring. Internal Jugular Vein cannulation was done and baseline parameters i.e. Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure, SpO_2 were noted. All emergency drugs were prepared.

After Pre-Oxygenation with 100% Oxygen for 3 minutes, Induction dose of 0.3mg/kg I.V. Etomidate given in Group A patients over 20 seconds. In group B patients priming dose 0.03mg/kg I.V. Etomidate was given followed after one minute by induction dose of 0.3mg/kg I.V. Etomidate given over 20 seconds. All patients were observed for Etomidate Induced Myoclonus (Primary endpoint) by an independent Observer for 3 min from the start of injection of the induction dose of Etomidate.

The Time of onset of Myoclonus was observed and categorise: within 1 min, 1 to 2 min, 2 to 3 min from the start of induction. The Intensity of Myoclonus was graded as: 0- No Myoclonus, 1- Mild Myoclonus (Short contractions of some muscle fibres e.g. finger, wrist), 2- Moderate Myoclonus (Contractions of two different groups of muscles e.g. face and arm), 3- Severe Myoclonus (Intense clonic movement in two or more muscle groups e.g. fast adduction of limb or whole body). The Time of Loss of Consciousness (LOC) was defined as the time from starting of the induction dose of Etomidate to the loss of response to verbal commands (Patient does not open eye on verbal command) noted. Loss of Consciousness (LOC) dose was defined as the dose of Etomidate administered to cause loss of consciousness.

3 minutes after the start of induction with Etomidate, patients in both groups were given injection Fentanyl 4mcg/kg followed by

injection Rocuronium(1mg/kg) to facilitate tracheal intubation. Positive pressure ventilation was given by using bag and mask for 90 seconds. Patients were intubated with appropriate size of Endotracheal Tube with the help of Direct Laryngoscopy. Anaesthesia was maintained with loading dose of Vecuronium Bromide 0.1mg/kg I.V. followed by 0.02mg/kg I.V. every 20 minutes along with Isoflurane 0.6-0.8 MAC.

The time for loss of consciousness was noted. Heart Rate, Blood Pressure, Mean Arterial Pressure and Peripheral Oxygen Saturation were recorded every minute from induction until tracheal intubation and 1, 3 and 5min after tracheal intubation (Secondary endpoints). Intraoperative monitoring was done throughout the surgery. At the end of surgery patients were shifted to cardiac ICU with ET tube in situ.

RESULTS

There was no statistically significant difference between the two groups in terms of age, sex and weight (Table 1). This helped us to judge the clinical significance of our study as distribution, metabolism, excretion and action of drugs are undoubtedly varied in different age groups. The mean time taken for loss of consciousness in control group was 30.23±3.33 seconds as compared to 31.19±2.57 seconds in priming group B. Statistical analysis shows that difference was non-significant between the two groups (P >0.005) (Table 1). The mean dose at which loss of consciousness occurred was 16.69±2.00 mg in control group as compared to 17.26±1.92 mg in priming group B. On statistical analysis, the difference between the two groups was found to be non-significant (Table 1).

Table 1. Demographic Profile and Induction Characteristics of both Study Groups

	Group A (n=54)	**Group B (n=54)**	**P value**
Age (years)	44.02±14.16	43.96±13.24	1.00
Sex (M/F)	29/26	32/22	0.621
Weight (kg)	60.22(8.99)	60.43(8.90)	0.906
LOC dose (mg)	16.69(2.00)	17.26(1.92)	0.131
LOC time(s)	30.20(3.33)	31.19(2.57)	0.089

Values are mean (SD) or number. Group A: control group, Group B: priming group, LOC dose: loss of consciousness dose, LOC time: loss of consciousness time.

The incidence, severity, and time of onset of myoclonus in both groups were as shown in Table 2.

Table 2. Characteristics of Myoclonus in Both Study Groups

Myoclonus	**Group A (n=54)**	**Group B (N=54)**	**P value**
Incidence	45 (83.33)	27 (50)	0.048
Severity grade			
0 (none)	9 (16.67)	27 (50)	
1 (mild)	8 (14.81)	12 (22.22)	
2 (moderate)	19 (35.19)	8 (14.81)	<0.001
3 (severe)	18(33.33)	7 (12.96)	
Time of onset(min)			
<1	17 (37.78)	11 (40.74)	
1-2	16 (35.56)	9 (33.33)	0.928
2-3	12 (26.67)	7 (25.93)	

Values are number of patients (%). Group A: control group, Group B: priming group.

The incidence of EIM in the priming Group was 50% (27/54) which was significantly lower than in the control Group 83.33% (45/54). Statistical analysis shows that the difference was significant between the study groups (P<0.005).

The severity of myoclonus was less in Group B as compared to Group A and the difference was statistically significant (P<0.05).We found that the percentage of patients who experienced moderate or severe EIM was significantly lower in Group B than in Group A. 22.22% of patients in Group B had grade 1 myoclonus as compared to 14.81% in Group A. 14.81% of patients had grade 2 myoclonus in Group B as compared to 35.19 in Group A. 12.96% of the patients had grade 3 myoclonus in Group B as compared to 33.33% in Group A.

We found in our study that the onset of myoclonus occurred within 2 min from the start of induction in 73.33% (33/45) patients of Group A and in 74.07% (20/27) patients in Group B, with no significant difference between the two groups. Both the groups were comparable in terms of the baseline pre-operative haemodynamic parameters of patients which were statistically not significant.

Compared with baseline values, The Mean Arterial Pressure (Fig. 1), Systolic Blood Pressure, Diastolic Blood Pressure and Mean Heart Rate (Fig. 2) decreased after induction of anaesthesia and increased after intubation in both groups. This increase was more at 1 min after intubation and the Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean

Arterial Blood Pressure then decreased at 3 min and 5 min after intubation, There were statistically non-significant differences in haemodynamic parameters at different time intervals after induction and intubation in both groups (P>0.005).

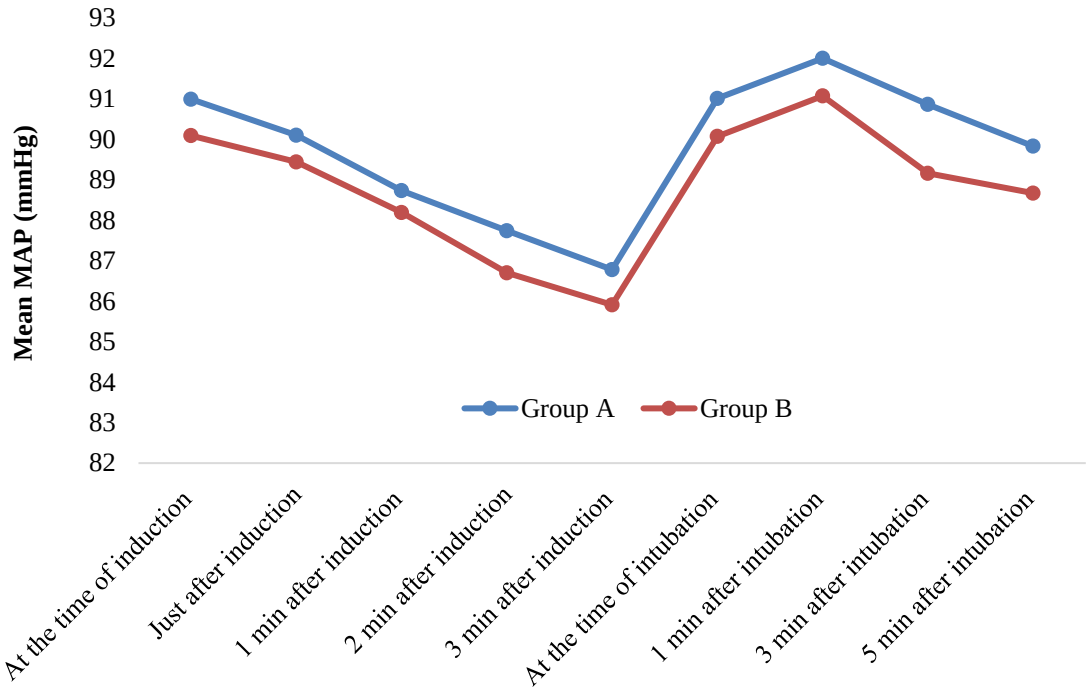

Fig.1. Mean arterial pressure (MAP) changes at various time points in both study groups.

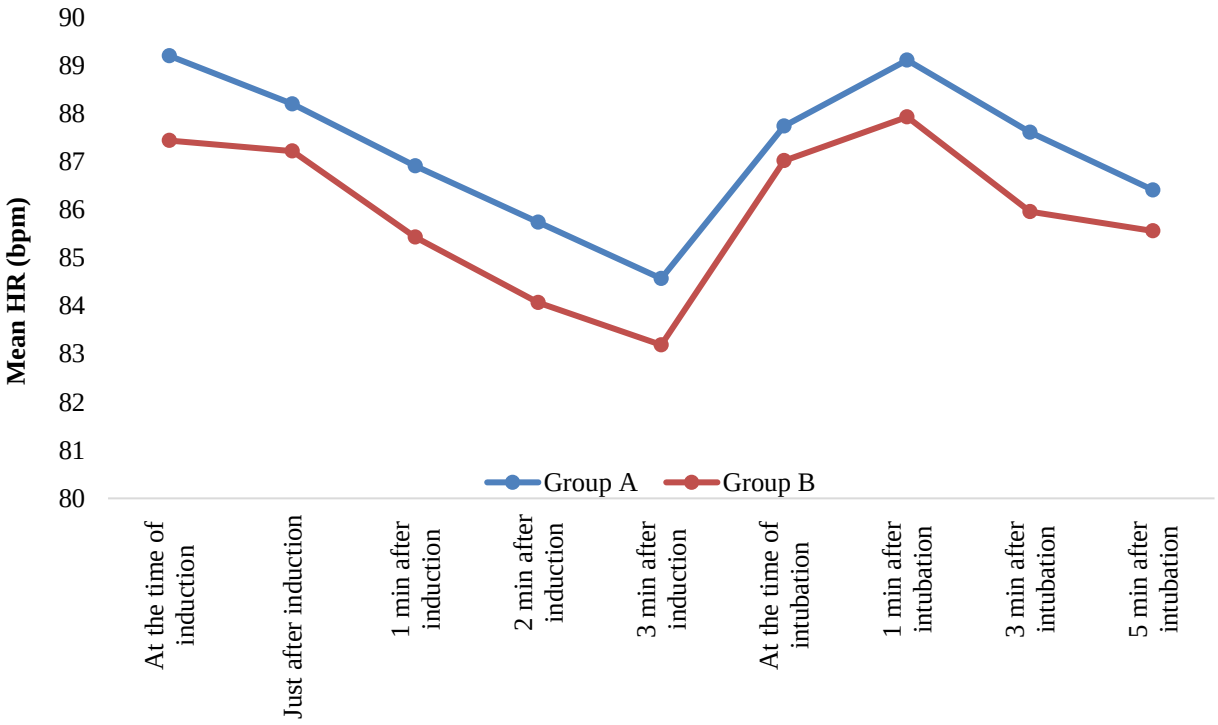

Fig. 2. Heart rate (HR) changes at various time points in both study groups.

DISCUSSION

Etomidate is widely used as an intravenous anaesthetic agent due to rapid onset of action, clearance and stable haemodynamic profile with minimal respiratory effects. Myoclonus is a common problem in induction of general anaesthesia with etomidate. The involuntary myoclonic movements seen with etomidate are believed to be caused by sub cortical disinhibition [4]. A large dose of etomidate depresses the cortical activity before depressing subcortical activity, thereby causing myoclonus [8-10]. Etomidate acts at the GABA A receptors. High doses of etomidate interacts with GABA A receptors of central nervous reticular activating system and directly activates the receptors, however lower doses have a modulating effect. The ability to modulate and activate GABA A receptors depends on the β-subunit type of the receptor. Therefore, the different distribution of GABA A receptor subunits within the CNS explains the reason of a regionally distinct effect of the drug. It is indicated that inhibitory circuits are depressed sooner and at lower doses of etomidate than excitatory circuits. Therefore, it is thought that pre-treatment with etomidate could diminish myoclonus related to the drug. Conversely, large bolus doses of etomidate leads to increased myoclonus [4,11].

There was no statistically significant difference between the two groups in terms of age, sex and weight. This helped us to judge the clinical significance of our study as distribution, metabolism, excretion and action of drugs are undoubtedly varied in different age groups. Therefore clinically insignificant variation in age, sex and weight helped us to alleviate these confounding factors. Both the groups were comparable in terms of the baseline pre-operative haemodynamic parameters of patients which were statistically not significant. Compared with baseline values, the mean heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure decreased after induction of anaesthesia and increased after intubation in both groups. This increase was more at 1 min after intubation and the heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure then decreased at 3 min and 5 min after intubation, There were statistically non-significant differences in haemodynamic parameters at different time intervals after induction and intubation in both groups (P>0.005). Our findings were in concordance with the findings of Mullick *et. al* (2018) [2] who compared two injection techniques slow injection versus priming with etomidate in reducing myoclonus. They found that there was statistically non-significant difference in haemodynamic parameters.

However our results do not match with the study done by Aissaoui *et. al* [6] in forty six ASA physical status I – II patients scheduled for elective abdominal surgery. The patients were allocated randomly to receive either pre-treatment 0.03 mg/kg of etomidate (priming group) or placebo (control group). Sixty-seconds after the pre-treatment, anaesthesia was induced with etomidate 0.3 mg/kg and 60 seconds later induction was completed with fentanyl (3 microg/kg) and vecuronium (0.1 mg/kg). The baseline haemodynamic parameters were comparable in between the two groups and there were statistically significant changes in haemodynamic parameters at different time intervals after induction and intubation.

In our study, the incidence of EIM in the priming Group was 50% (27/54) which was significantly lower than in the control Group 83.33% (45/54). Our study validates the findings of Mullick et al. [2] who observed that priming is more effective (60%) than slow injection (90%) in reducing the incidence of myoclonus. As per their study, the incidence of myoclonus in Priming Group (38/63 [60.3%], 95% CI: 48.0–71.5) was significantly lower than in Control Group (53/63 [84.1%], 95% CI: 72.9–91.3, P = 0.003) and slow injection Group (49/63 [77.8%], 95% CI: 66.0–86.4, P = 0.034). Myoclonus of moderate or severe grade occurred in significantly more patients in Control Group (68.3%) as compared to Priming Group (36.5%, P < 0.001) and Slow injection Group (50.8%, P = 0.046), but the difference between Priming and Slow injection Group was statistically not significant (P = 0.106).

Another study by Aissaoui *et. al* [6] also validate our findings. They observed a significant reduction in the incidence of myoclonic movements following priming with a low dose of etomidate. In their study 26 % (6/23 patients) of patients in the priming group experienced myoclonus as compared to 87% (20/23 patients) in the control group (P< 0.001). Doenicke *et. al* [4] found that the incidence of EIM was 25% (2/8 patients) when etomidate induction followed pre-treatment with 0.05 mg/kg etomidate, as compared to 75% (6/8 patients) in the control group. Do *et. al* [7] observed that slow injection of etomidate (over 2 min) resulted in a significantly lower incidence of EIM (28% [7/25 patients]) than giving it as a fast injection over 10s (84% [21/25 patients], P < 0.001). However we found a higher

incidence of EIM in the priming group than reported by some other studies [4, 6]. This could perhaps be due to the fact that we did not pre-medicate our patients and administered a muscle relaxant 180 sec after the start of induction, thus allowing a longer time period for observation of myoclonus.

In contrast Doenicke et al [4] pre-medicated their patients with oral midazolam 1 h prior to induction and administered a muscle relaxant 90 seconds after induction, allowing a shorter time period for observation than ours. Aissaoui et al [6] also used a smaller time period for observation, as they administered a muscle relaxant 60 seconds after induction with etomidate.

Our study showed that incidence of myoclonus was more in Group A (83.33%) as compared to Group B (50%).

In Group A 14.8% of patients had grade 1 myoclonus as compared to 22.22% patients in Group B.

In Group A 35.19% of patients had grade 2 myoclonus as compared to 14.81% patients in Group B.

In Group A 33.33% patients had grade 3 myoclonus as compared to 12.96% patients in Group B.

We found that the percentage of patients who experienced moderate or severe EIM was significantly lower in Group B than in Group A.

Our findings are in concordance with Aissaoui *et. al* [6] who also found the severity of myoclonus to be significantly lower with priming group than in control group. Our findings are supported by Mullick *et. al* [2] who observed that priming is more effective than slow injection in reducing the incidence of myoclonus. We found in our study that the onset of myoclonus occurred within 2 min from the start of induction in 73.33% (33/45) patients of Group A and in 74.07% (20/27) patients in Group B, with no significant difference between the two groups. Our results are supported by study done by Mullick *et. al* [2] in which there was no difference in mean LOC dose between Group P and Group C and also there was no difference in mean time until LOC between Group P and Group C. Aissaoui *et. al* [6] found that the average dose of etomidate used during the induction was similar between the 2 groups (0.29±0.032 mg/kg in the priming group and 0.30±0.029 mg/kg in the control group).

The time until loss of consciousness (LOC) was defined as the time from start of injection of the induction dose of etomidate until loss of response to verbal commands (eg. patient does not open eye on verbal command).

In our study, mean time taken for loss of consciousness in group A was 30.20±3.33 seconds as compared to 31.19±2.57 seconds in group B. Statistical analysis shows that difference was non-significant between the two groups (P >0.005).

LOC dose was defined as the dose of etomidate (mg) after which loss of consciousness was observed.

Mean dose at which loss of consciousness occurred was 16.69±2.0 mg in group A as compared to 17.26±1.92 mg in group B.

On statistical analysis, the difference between the two groups was found to be non-significant (P>0.005).

Our results are supported by study done by Mullick *et. al* [2] in which there was no difference in mean LOC dose between Group P and Group C and also there was no difference in mean time until LOC between Group P and Group C. Another study by Aissaoui *et. al* [6] found that the average dose of etomidate used during the induction was similar between the 2 groups (0.29±0.032 mg/kg in the priming group and 0.30±0.029 mg/kg in the control group). In the majority of the patients in our study, the onset of myoclonus occurred within 2 min after the start of induction. The period of observation for myoclonus varied from 1 to 3 min in most previous studies, suggesting that the actual incidence of EIM may be higher than that reported. Delayed myoclonic movements could go undetected due to masking by a neuromuscular blockade. To determine the true incidence of EIM, further studies are needed to identify the optimal period. None of the patients showed other side effects like nausea, vomiting, pain on injection, hiccups etc.

It was not a blind study.

The time of onset of myoclonus was categorized into 1-min intervals from the start of induction. Thus, the exact time of onset and duration of myoclonus was not noted. Duration was a limiting factor, we observed myoclonus only till 3 min from start of induction, so actual incidence may be higher. We selected only 54 patients in each group, might require more patients in both groups for better results.

CONCLUSION

The present study was conducted in 108 patients of either sex, between 20-60 years of age, scheduled for cardiac surgeries under general anaesthesia and it was concluded that priming with etomidate significantly reduced the incidence and severity of myoclonus.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Kanchan Chauhan contributed in conception of work and study design. Mukesh K Sunda performed experimental work and collected data. Rajeev performed statistical analysis. Krishna contributed in interpretation of collected data. All the authors helped in proofreading and reviewing the final manuscript

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