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Pretreatment with Three Different Doses of Lignocaine to Prevent Etomidate Induced Myoclonus

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Abstract

Introduction: Myoclonus is a common problem during induction of anesthesia with etomidate. We evaluated the effect of Lignocaine pretreatment on the incidence and severity of myoclonus in our study. *Methods:* This is a prospective randomized double blind study. Sample size was calculated with power of study 80% and alpha error 5%, 96 patients of ASA physical status I and II, aged 18 to 60 years scheduled for elective surgery under general anesthesia were included into three groups L1, L2, L3. Before induction, patients were pretreated with inj. 2% lignocaine 3 ml containing 40 mg, 50 mg, 60 mg diluted with normal saline depending on the random allocation by computer generated random number table. Patients were induced with 0.3 mg/kg etomidate within 30–60 sec, one minute after pretreatment with lignocaine. Patients were observed continuously for the time of initiation, grade and severity of myoclonus for 90 sec, *Results:* In our study, it was found that with Injection 2% lignocaine 60 mg IV 59.3%, 50 mg Lignocaine 37.5%, 40 mg Lignocaine group 9.3% of the patients had no myoclonus which was found to be significant $p < 0.001$. *Conclusion:* Both 2% IV Lignocaine 50 mg and 60 mg were effective in reducing the severity of myoclonus induced by Etomidate without causing side effects.

Keywords: Pretreatment Etomidate; Lignocaine; Myoclonus; Hemodynamics.

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Introduction

The intravenous route of the administration of drugs was long ago recognized as being the most convenient means for obtaining general anesthesia. In fact, the efficacy of this method was appreciated long before a suitable agent was available with the result that intravenous anesthesia awaited only the development of an ideal agent.

Ideal intravenous anesthetic agent for the induction of general anesthesia with all the desirable characteristics like stable in solution, absence of pain on injection, no histamine release, cadiovascular stability, rapid onset and complete return of consciousness and also absence of postoperative effects like nausea, vomiting, delirium, headache is yet to be developed.[1]

Etomidate is an imidazole-derived, sedative hypnotic agent. It acts directly on GABA receptor complex, blocking neuro excitation and producing anesthesia.

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Etomidate causes minimal histamine release and has a very stable hemodynamic profile. Etomidate's hemodynamic stability is due to its unique lack of effect on the sympathetic nervous system and on baroreceptor function. Even in cardiac patients induction dose of etomidate results in very stable hemodynamic. Etomidate has minimal effects on respiratory system also as compared to other induction agents and can be safely given in patients with reactive airway disease. However, pain on Injection and myoclonus are the most common side effects of this drug.[2] Pain on injection has been abolished by the new fat emulsion preparation of etomidate, but the new solvent has not reduced the incidence of myoclonus.[3] Myoclonus is a common problem during induction of anesthesia with etomidate, upto 80% of the nonpremedicated patients develop myoclonic movements[4], which maybe a problem in the nonfasting patients because of the risk of hypoventilation as well as regurgitation and aspiration.[5,6] Myoclonic movements may even raise the risk of prolapse of the vitreous in patients with open globe injury.[7] Although the probable mechanism of etomidate induced myoclonus is alteration in the balance of inhibitory and excitatory influence on the thalamocortical tract[4], a number of drugs have been investigated for their ability to suppress these myoclonic movements. Pretreatment with benzodiazepines (28%)[4], opioid (17%)[5], and Rocuronium (25%)[6] have been shown to reduce myoclonus to some extent. However, the drug of choice to prevent myoclonus induced by Etomidate is yet to be discovered.

Ideally, a pretreatment drug for preventing myoclonic movements should be short acting, should not have significant effects on respiration and hemodynamics, and should not prolong recovery from anesthesia[4] Lignocaine stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses and has rapid onset of action. Lidocaine alters signal conduction in neurons by blocking the fast voltage gated Na+ channels in the neuronal cell membrane responsible for signal propagation.[8] The aim of our study, was to find the optimum dose of pretreatment with intravenous 2% lignocaine and to compare the incidence and severity of myoclonic movements along with any other side-effects linked to Etomidate.

Materials and Methods

A randomized, double blind clinical study protocol was approved by institutional ethical committee. Patients aged between 18 and 60 years with BMI of 20–25 kg/m^2, the American Society of Anesthesiology (ASA) physical status I and II undergoing elective surgery under general anesthesia were assigned to three groups, each containing 32 patients. Patients who were allergic to 2% lignocaine, on sedatives/opioids within 24 hours before surgery, patients with adreno cortical disorders, neurological, psychiatric disorders were excluded from the study. Patients underwent preanesthetic evaluation prior to surgery and nil per oral orders were followed. Alprazolam 0.5 mg given night before surgery. Antacids Inj. Ranitine 150 mg given 1 hour before surgery.

In our study, 96 patients were randomly allocated into three groups 32 patients in each group by computer generated random number table. Monitors like Noninvasive Blood Pressure (NIBP), Electrocardiography (ECG), pulse oximetry (SpO_2) and End Tidal Carbon Dioxide ($EtCO_2$) monitors were connected. Intravenous fluids were given according to the body weight of the patient and surgical loss. Group L1 received 40 mg 2% lignocaine diluted with 1 ml of normal saline, Group L2 received 50 mg 2% lignocaine diluted with 0.5 ml of normal saline, Group L3 received 60 mg 2% lignocaine. Patients were preoxygenated with 100% oxygen for 3 minutes. One min after pretreatment patients were induced with 0.3 mg/kg etomidate within 30–60 sec and were observed for the grade and severity of myoclonus for 90 sec. After administration of Etomidate and evaluation of myoclonus, all patients were injected with 2 mcg/kg Fentanyl, Inj. 0.05 mg/kg Midazolam, 0.1 mg/kg Vecuronium to facilitate tracheal intubation. Maintenance of anesthesia was provided by N_2O:O_2 5:3 along with Inj. Vecuronium 0.025 mg/kg plus Sevoflurane MAC of 1.5-3%. Study drugs were prepared in 5 ml syringes by coding them into three groups A, B, C and were decoded after 24 hours of observation byAnesthetist not participating in the study and were administered 1 min before induction with 0.3 mg/kg etomidate (Triomidate Troikaa) by some another anesthetist not participating in the study thus observer and the patient were blinded. The time to the loss of eye-lash reflex was recorded as the onset of induction, and an additional dose of etomidate was administered if necessary. Patients were observed continuously for the grade and severity of myoclonus for 90 sec. Vital signs pulse rate, blood pressure, ECG, SpO_2, $EtCO_2$ were monitored 1 min and 3 min after etomidate injection. Intraoperatively continuous hemodynamics monitoring was done. Postoperatively after thorough oral suction patients

was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01 mg/kg. Tracheal extubation was performed on meeting the standard criteria of extubation. Postoperatively patients were assessed for 24 hrs for myalgia, headache, nausea and vomiting.

The Primary objective of this study, is to find the optimum dosage of Lignocaine required to prevent myoclonus and the secondary objective is to find the reduction in severity of Etomidate induced myoclonus, hemodynamic stability after induction of Etomidate.

Myoclonic movements are graded clinically as 0 = no myoclonus, 1 = mild myoclonus (short movement of a body segment, e.g.: a finger or 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 adduction of a limb. Nausea and vomiting were assessed as 0 = no symptom, 1 = symptom present but treatment not required, 2 = symptom present and treatment given. Any other side effect of Etomidate like myalgia and headache were also noted upto 24 hours.

A power analysis based on article by Kahlon Singh et al. states that 66 patients are required to have 80% chance of detecting as significant at 5% level, a decrease in primary outcome measures myoclonus from 76% in the control group to 44% in the lignocaine groups, assuming the same decrease in the primary outcome, in a dose response to lignocaine with increasing strength of lignocaine a sample size of 96 patients of ASA physical status I and II of age group between 18 and 60 years scheduled for elective surgeries under general anesthesia were allocated to three groups n = 32 randomly after taking informed written consent.

The data was entered in Microsoft Excel and analyzed in EpiData analysis V2.2.2.184, Stata 12 and SPSS 20 software. The continuous variables such as age, height, weight, Body Mass Index, baseline value, 3 minutes and 5 minutes after induction vital parameters values (pulse rate, blood pressure), SpO_2 and time for myoclonus were reported as Mean (SD) or median (Inter Quartile Range) based on distribution of data. The categorical variables such as Group (L1, L2 and L3), gender, grading of severity of myoclonus, nausea, vomiting, post operative myalgia and headache were reported as proportions. The association between continuous variables and the Groups (L1, L2 and L3) were assessed using one way ANOVA or Kruskal Wallis test and the association between categorical variable and groups were assessed using Chi-square test. The difference between the groups over the time points and difference within the groups were measured using repeated measures of ANOVA. The p - value of < 0.05 was considered for statistical significance.

Results

Demographic data concerning patient's age, weight, BMI were comparable among all three groups. In our study, female population was comparatively (52%) more than the male population (48%) which was found to be significant $p < 0.001$. There was a significant ($p < 0.001$) height difference among the study population. Hemodynamic parameters from baseline value, 3 min and 5 min postinduction with Etomidate were comparable among the three groups $p > 0.005$. Time for myoclonus among the study participants in each group after induction in our study was not significant $p = 0.071$ (Table 1 and Fig. 1). Comparing the three groups the reduction in the severity of myoclonus postetomidate induction with lignocaine pretreatment was found to be significant $p < 0.001$ (Table 2 and Fig. 2). The incidence of postoperative nausea and vomiting in three groups was significant $p < 0.004$ (Table 3 and Fig. 3). There was no significant postoperative myalgia and headache with $p < 0.364$.

Table 1. Time for myoclonus among the study participants in each group after induction (N = 96)

Group	Number	Median (IQR) time for myoclonus (sec)	Range	*p* value*
L1	32	37.87 (20.7-62.3)	0-78.87	
L2	32	33.17 (0-59.2)	0-86.78	0.071
L3	32	7.56 (0-57.0)	0-90	

** Kruskal Wallis test*

The table 1 shows the comparison of time of initiation of myoclonus in all the three groups was insignificant $p = 0.071$.

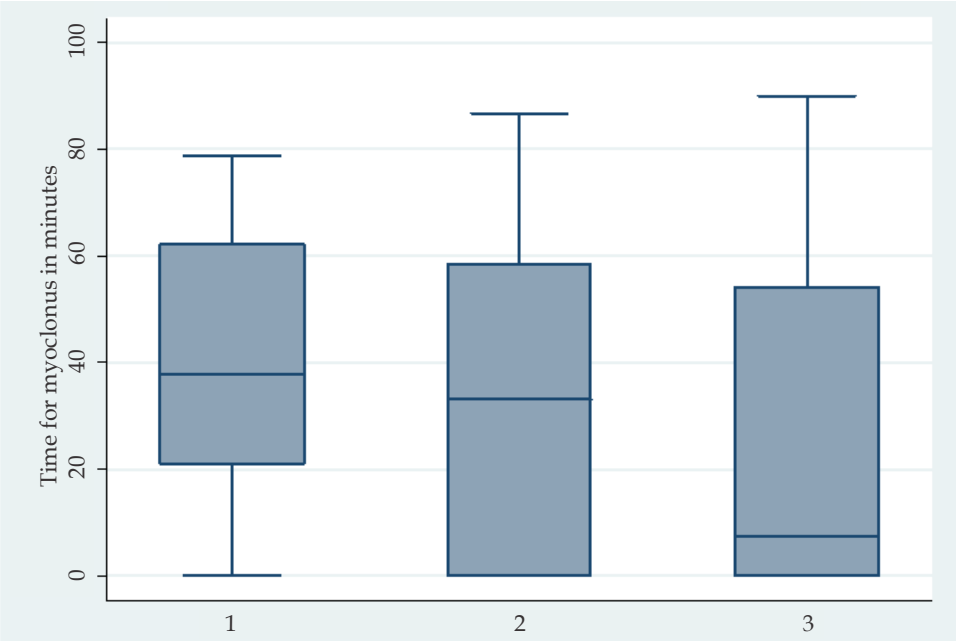

Fig 1: Time for myoclonus among the study participants in each group 5 minutes after in duction (N = 98)
**1,2,3 in X axis denotes group L1, L2 and L3 respectively*

Table 2. Severity of myoclonus among study participants in each group:

Groups	Number	Grade 0		Grade 1		Grade 2		Grade 3		*p* value#
		n	%	n	%	n	%	n	%	
L1	32	3	9.3	14	43.7	12	37.5	3	9.3	
L2	32	12	37.5	14	43.7	5	15.6	1	3.1	0.001
L3	32	19	59.3	5	15.6	8	25	0	0.00	
Total	96	34	35.4	33	34.3	25	26	4	4.1	

#chi square test

The table 2 shows the comparison of severity of myoclonus among the three groups L1, L2, L3 which was significant $p < 0.001$.

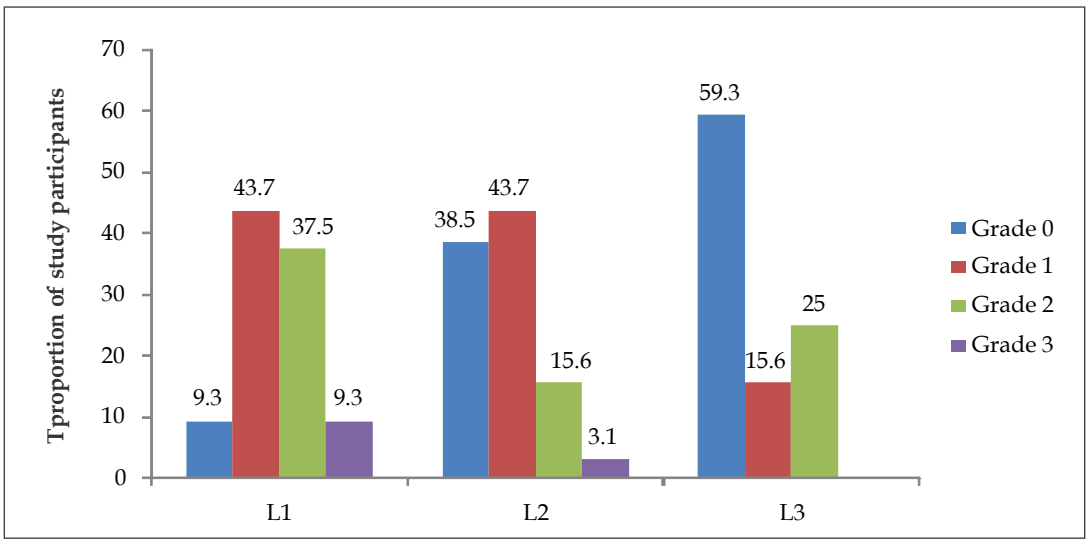

Fig 2: Severity of myoclonus among study participants in each group (N = 96)

Table 3. Severity of post-operative nausea and vomiting among study participants in each group

Groups	Number	Grade 0		Grade 1		Grade 2		*p* value#
		n	%	n	%	n	%	
L1	32	17	28.3	10	50.0	5	31.3	
L2	32	18	30.0	8	40.0	6	37.5	0.004
L3	32	25	41.7	2	10.0	5	31.3	
Total	96	60	100.0	20	100.0	16	100.0	

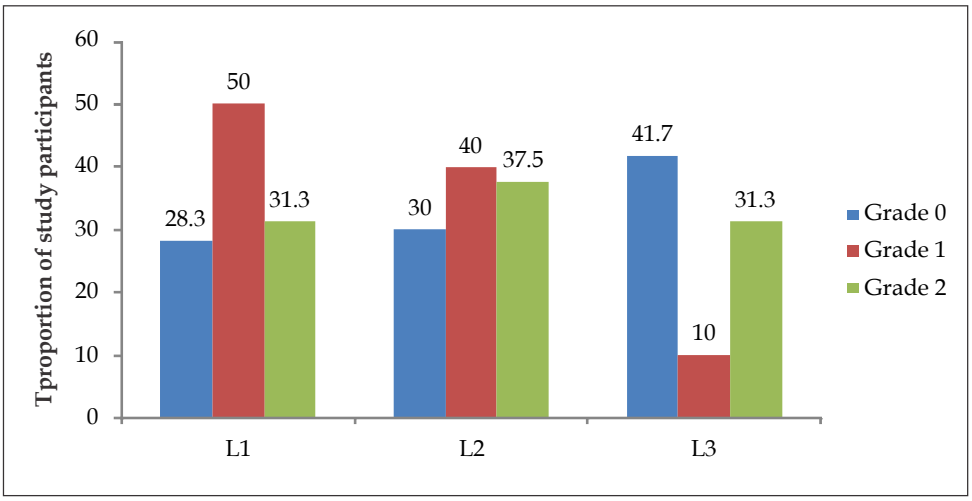

Fig 3: Severity of post-operative nausea and vominting among study participants in each group (N = 96)

Discussion

In this randomized double blind prospective clinical study, we compared the effects of different dose response of Lignocaine pretreatment on the incidence of etomidate induced myoclonus. To the best of our knowledge, there is shortage of literature studying Lignocaine pretreatment for etomidate induced myoclonus. Most of these studies have been done with 20 mg of Lignocaine IV in patients posted for elective surgery.

Etomidate is widely used as an induction agent in clinical practice. Several desirable properties, such as rapid onset, brevity of action, cardiovascular stability, protection of intracranial pressure, minimal histamine release, minimum respiratory depression and profound hypnosis makes it an ideal induction agent. However, etomidate is also associated with minimal side effects like pain on injection and myoclonus. Pain on injection has been largely eliminated by use of a lipid formulation of etomidate, but myoclonus remains a common problem during anesthesia induction.[4]

Ideally, a pretreatment drug for preventing myoclonic movements should be short-acting, should not have significant effects on respiration and hemodynamics and should not prolong recovery from anesthesia. Kahol et al. 1 in their study showed that 20 mg of Inj. 2% Lignocaine showed 56% reduction in the incidence of myoclonus.[9] Similar results were observed in the study by Gultop et al. Inj. 2% lignocaine (1 ml) and saline, was administered 30 sec before induction with etomidate, and it was observed that there was 56.6% incidence of myoclonus in the lignocaine group compared with 83% in the control group.[10] However, the mechanism by which lignocaine prevents myoclonus is unclear. Nyman and colleagues speculated that lignocaine reduces the excitability of the central nervous system, which is the cause of myoclonic movements.[2] In our study, we chose to compare escalating dose of 2% IV Lignocaine for reducing the severity of myoclonus as it does not have respiratory depression property unless toxic dose is given, is hemodynamically stable, helps in faster recovery from anesthesia as ithas antiinflammatory and analgesic properties.

We did not include control group in our study since it has already been proven that upto 80% of the patients develop myoclonus after induction with etomidate.[9,5] Thus, it would be unethical to subject the patients to myoclonus. Myoclonus may

be a problem in the nonfasting patient because of the risk of hypoventilation as well as theoretically regurgitation and aspiration[7] can occur. In patients with an open globe injury, myoclonus after etomidate raises intraocular pressure which increases the risk of vitreous prolapsed.[7] The study population included adult patients (18 to 60 years of age) of either sex, ASA Grades I and II undergoing elective general surgeries under general anesthesia who were randomly divided into three groups of 32 patients each.

There was no significant difference between the three groups regarding age, weight, BMI. In our study, female population was comparatively (52%) more than the male population (48%) which was found to be significant $p < 0.001$. There was a significant ($p < 0.001$) height difference among the study population because females were more than males in the study group. All the study population belonged to younger age group of 20 to 44 years. It was seen that there was not much change in the hemodynamic parameters from the baseline values, 3 min and 5 min postetomidate 0.3 mg/kg induction. These results have been further supported by Kahlon et al.[9] Huter et al.[6] and Lee et al.[11]

Various drugs have been used for reducing incidence and severity of myoclonus during IV injection of etomidate. Pretreatment with diazepam or flunitrazepam could not reduce myoclonus,[12] but midazolam reduced the incidence due to its faster onset of action.[4] Doenicke et al., reported that pretreatment with three different dosages (etomidate 0.03, 0.05 or 0.075 mg/kg IV) of etomidate used as premedicant reduced myoclonus.[4] Although studies have shown that fentanyl, alfentanil, or sufentanil are effective in reducing myoclonus, but these agents may cause residual apnea, sedation, nausea, vomiting, and delayed discharge from the hospital. Another study showed Remifentanil (1 µg/kg^{-1}) has faster onset of action, was very effective in reducing myoclonus after etomidate from 70% in the placebo group to 6.7% in the remifentanil group.[14] However, Remifentanil can cause severe bradycardia. Mizrak et al. concluded that pretreatment with dexmedetomidine or thiopental is effective in reducing the incidence and severity of etomidate-induced myoclonic muscle movements. Incidence of myoclonus was significantly low in Dexmedetomidine and Thiopental groups (34%, 36%) than in control groups (64%) ($p < 0.05$).[13] However, dexmetomidine can further cause hypotension and bradycardia, pretreatment with Thiopentone increases postoperative pain.[13]

In our study, the time of initiation of myoclonus was comparable among all the three groups. In our study, it was found that with Injection 2% lignocaine 60 mg IV, 59.3% of the patients in the group had no myoclonus. In patients who received 50 mg Lignocaine 37.5% had no myoclonus and 40 mg Lignocaine group 9.3% of the patients had no myoclonus. In L1 , L2 and L3 group 43.7%, 43.7% and 15.6 % of the population respectively had Grade 1 myoclonus. Grade 2 myoclonus was found to be 37.5% in L1 Group,15.6% in L2, 25% in L3 Group. In L1 and L2 Group 9.3% and 3.1% respectively had Grade 3 myoclonus. None of the patients in L3 Group had Grade 3 (severe) myoclonus. Comparing the three groups the reduction in the severity of myoclonus postetomidate induction with lignocaine pretreatment was found to be significant $p < 0.001$. This variation in our study could be due to ethnic variations or selection of a younger age group. The factors known to affect the incidence of myoclonus are age (the higher the age, the lesser the chances of development of myoclonus), sex of the patient (incidence is higher among male individuals), and the dose of etomidate.[11,14] It can be concluded from the above results that higher dose of Lignocaine is highly efficacious in suppressing myoclonus during induction with etomidate without causing hemodynamic instability and respiratory depression.

Kahlon A Singh et al.[9] concluded that pretreatment with lignocaine or midazolam is effective in reducing the incidence and severity of etomidate-induced myoclonic muscle movements. Incidence of myoclonus was significantly low in Lignocaine and Midazolam groups (28% and 44% respectively) than in control groups (76%) ($p < 0.05$).

Gultop et al.[10] observed in their study that Inj. 2% lignocaine (1 ml) and saline, when administered 30 sec before induction with etomidate, showed 56.6% incidence of myoclonus in the lignocaine group compared with 83% in the control group which was found to be significant $p < 0.005$.

Therefore, the results of our study are in concordance with the other studies which finds lignocaine efficacious in suppressing etomidate induced myoclonus.

The incidence of postoperative nausea and vomiting in three groups was significant $p < 0.004$. Around 30–38% patients in each group required treatment with antiemetics. Giese and colleagues[15] found the incidence of postoperative nausea and vomiting to be significant $p < 0.005$, when they used etomidate in their study.

The incidence of severity of postoperative myalgia and headache was found to be insignificant. No other side-effects of Etomidate was found in our study.

The absence of any recording of the electromyograph, time duration of myoclonus, incidence of myoclonus in extremes of age group after induction with etomidate, constant drug dosage was a limiting factor for our study. The present study was conducted with a fixed drug dosage instead lignocaine as pretreatment drug can be given according to the body weight which can further reduce the incidence and severity of myoclonus postetomidate induction.

Conclusion

In our study we found that both 2% IV Lignocaine 50 mg and 60 mg were effective in reducing the severity of myoclonus induced by Etomidate without causing any side effects. It was found that Lignocaine 60 mg to be more effective. Hence, with the escalating dose of Injection 2% Lignocaine IV within the toxic dose can limit myoclonus caused by Etomidate induction. However, more number of independent studies will prove it's efficacy.

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