

Effect of Lidocaine Pre-Treatment on Myoclonus during Induction of Anaesthesia with Etomidate- A Randomised, Double-Blind, Placebo-Controlled Study

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ABSTRACT

BACKGROUND

Etomidate is widely used for induction of general anaesthesia and sedation, especially in elderly patients and hemodynamically unstable patients. However, myoclonus is one of the most prominent problems encountered during induction of anaesthesia with etomidate. Many agents have been used to prevent it including lidocaine. This prospective, randomised controlled study was taken up to evaluate the effect of pre-treatment with lidocaine versus placebo on the incidence and severity of myoclonus at one minute and two minutes after induction of anaesthesia with etomidate for elective surgeries.

METHODS

One hundred adult patients were randomly assigned into two groups to receive saline placebo (Group I) and IV lignocaine 1 mg/Kg (Group II). Group I (n=50) received 6 ml of normal saline (placebo) and Group II received lidocaine, 1 mg/Kg, diluted with normal saline up to 6 ml. Double blinding was achieved by making the principal investigator and the patient unaware of which drug was given. Two minutes after administering the study drug, intravenous etomidate (Troymidate, Troikkaa) 0.3 mg/Kg was administered over 30 seconds and the patient was monitored for myoclonus over the next two minutes.

RESULTS

At one-minute, myoclonus was seen in 34 patients (68%) and 15 patients (30%) respectively in Group-I and Group-II. There was a statistically significant reduction in the incidence of myoclonus at one minute in Group-II compared to Group-I ($p<0.05$). At two-minutes myoclonus was seen in 32 patients (64%) and 19 patients (38%) respectively in Group-I and Group-II. There was a statistically significant reduction in the incidence of myoclonus at two minutes in Group-II compared to Group-I ($p<0.05$).

CONCLUSIONS

Lignocaine 1 mg/Kg pre-treatment significantly reduces the incidence of Etomidate induced myoclonus (EM) compared with the control group.

KEYWORDS

Anaesthesia, Etomidate, Lidocaine, Myoclonus, Premedication

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BACKGROUND

A very vital and important step in commencing general anaesthesia is choosing the induction agent. Etomidate, a carboxy-imidazole derivative was introduced in 1973 for the first time as an induction agent due to its low cardiopulmonary side effects and minimal histamine releasing effects.^{1,2} The haemodynamic stability of etomidate is unique and onset of anaesthesia after a routine induction dose of 0.3 mg/Kg of etomidate is rapid (one arm brain circulation).³ Its other desirable properties are rapid onset of profound hypnosis, haemodynamic stability, minimal respiratory depression and favourable cerebral effect. It is therefore preferred in haemodynamically unstable patients due to these properties.⁴ Subsequently, it was soon observed that etomidate causes pain in injection site, postoperative nausea and vomiting, electroencephalographic activity, adrenal suppression and myoclonus.⁵ Myoclonus is the visible muscular contractions occurring due to involuntary contractions of muscle fibres.⁶ Myoclonus related with etomidate use occurs in 50 to 80% of patients.⁷ Etomidate induced myoclonus may vary from innocuous movement at fingers to intense clonic movements. These involuntary movements may lead to muscle damage, myalgia, hyperkalaemia, accidental dislodgement of the vascular access and monitoring devices.⁸ The myoclonus may prove to be particularly hazardous in patients with open globe injury, full stomach, hypertension, coronary artery disease and intracranial aneurysm.⁸ The exact mechanism of the etomidate induced myoclonus is not known, however it is believed to be due to disinhibition of subcortical structures that normally suppress extra pyramidal motor activity.⁹ Another possible mechanism suggested was that the pathway related to skeletal muscle control became more sensitive to spontaneous nerve transmission once GABA neurons were disrupted, causing myoclonic muscle movements.¹⁰ Various drugs have been used as pre-treatment to reduce myoclonic movement like opioids (sufentanil, remifentanil), benzodiazepines (midazolam), magnesium sulphate, rocuronium, lidocaine.^{1,4,10,11} Lidocaine (Lignocaine) in low doses (20 mg) have been found to reduced etomidate induced myoclonus¹². Lidocaine is considered very close to being an ideal pre-treatment for the reduction of etomidate induced myoclonus because it has a rapid onset of action, short duration of action, minimal cardiorespiratory depression and does not prolong recovery from anaesthesia in the clinically used doses.⁴ The literature which evaluates the efficacy of lidocaine against etomidate induced myoclonus is scarce. Thus, this study was taken up to evaluate the effect of pre-treatment with lidocaine versus placebo on the incidence and severity of myoclonus at one minute and two minutes after induction of anaesthesia with etomidate for elective surgeries.

METHODS

This prospective, randomized, double-blinded study was carried out in the Department of Anaesthesiology, Regional Institute of Medical Science, Imphal, from September 2018 to August 2019. After obtaining written informed consent, 100 patients of either sex belonging to 18–60 years of age, the American Society of Anesthesiologists (ASA) physical status I or II and undergoing elective surgeries under planned general anaesthesia were included in the study. Patients with a history of allergy or contraindication to any of the study drugs (etomidate or lignocaine), anticipated difficult airway or difficult venous access, disorders of lipid metabolism, impaired renal or hepatic functions, known adrenal cortical dysfunction, psychiatric or neurological disorder, pregnant or lactating mothers, cardiac conduction abnormalities and patients on antiarrhythmic medications, or taking analgesic before surgery were excluded from the study. Approval from the institutional ethics committee were obtained. The patients recruited were randomly assigned to one of the two groups based on the randomization number which were generated using web based randomization list available at www.randomization.org. Group I (n=50) received 6 ml of normal saline (NS) (placebo) and Group II (n=50) received lidocaine (1 mg/Kg) diluted to 6ml with normal saline. Double blinding was achieved by making the principal investigator and the patient unaware of which drug was given. The study drug was prepared in identical syringes by a co-anaesthetist not involved in the observation of the study thereby preventing bias. Pre-anaesthetic evaluation was done in all the patients scheduled for elective surgeries. Detailed history, physical examination and basic investigations like haemoglobin, random blood sugar, blood urea, serum creatinine, serum electrolytes, chest X-ray (PA view) and electrocardiogram (ECG) were done. All the baseline vitals like non-invasive arterial blood pressure, heart rate, ECG and pulse oximetry were recorded. A suitable peripheral vein was cannulated for administration of anaesthetic agents and intravenous fluids. The anaesthetic regime was standardised for all the patients. Two minutes after administering the study drug, intravenous etomidate (Troymidate, Troikka) 0.3 mg/Kg was administered over 30 seconds and the patient was monitored for myoclonus over the next two minutes. After induction, the patient was ventilated with 100% oxygen using an appropriate size face mask. Myoclonic movements were observed, evaluated and graded according to clinical severity during the two minutes after etomidate injection. The intensity of myoclonus were graded clinically and severity assessed as Grade 0: No myoclonus, Grade-1: mild myoclonus (short movement of a body segment, e.g., finger or a wrist only), Grade 2: moderate myoclonus (mild movements of two different muscles, e.g., face and leg), Grade 3: severe myoclonus (intense myoclonic movements in two or more muscle groups, fast adduction of a limb).⁷ Depending on the time of onset, the presence or absence of myoclonus at one minute (EM-1) and two minutes (EM-2) were recorded. Fentanyl 2 µg/Kg intravenous and Rocuronium 0.6 mg/Kg intravenous

was administered after two minutes observation period or the onset of myoclonus whichever was earlier and mask ventilation was continued for 60 seconds. Tracheal intubation with an appropriate sized endotracheal tube was performed and anaesthesia was maintained with nitrous oxide and sevoflurane in oxygen. The patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 35-40 mmHg. The primary outcome variable for the study was the incidence of myoclonus at two minutes. The incidence of myoclonus at one minute and the severity of myoclonus was the secondary outcome variables for the study. The data collected were checked for completeness and consistency. Data thus collected were then analysed by using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Windows based version 21. In all analysis, the subjects were grouped according to which patients were randomly assigned (intention to treat analysis). Descriptive statistics like mean, standard deviation were used in variables like gender, age, weight and ASA. ANOVA was used to test the difference in the mean of gender, age, weight and ASA. Chi-Square test was used for comparing the difference in the incidence and grade of myoclonus among the two study groups and p value <0.05 was taken as significant.

Myoclonic movements were observed, evaluated and graded according to clinical severity during the two minutes after etomidate injection. Data thus collected were then analysed by using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Windows based version 21. Descriptive statistics like mean, standard deviation were used in variables like gender, age, weight and ASA. ANOVA was used to test the difference in the mean of gender, age, weight and ASA. Chi-Square test was used for comparing the difference in the incidence and grade of myoclonus among the two study groups and p value <0.05 was taken as significant.

RESULTS

A total of 100 patients meeting the inclusion criteria during the study period were included in the present study. These 100 patients were randomized into two groups of 50 patients each (Figure 1). Demographic characteristics (age, weight, sex and ASA physical status) were similar across the two groups. There was no statistical difference between the two groups with respect to the demographic characteristics (Table 1). The minimum and the maximum age in Group-I was 18 years and 60 years respectively, while it was 19 years and 60 years respectively in the group-II.

At one-minute, myoclonus was seen in 34 patients (68%) and 15 patients (30%) respectively in Group-I and Group-II. Myoclonus was absent in 16 cases (32%) and 35 patients (70%) in Group-I and Group-II respectively as shown in Table-2. There was a statistically significant reduction in the incidence of myoclonus at one minute in Group-II compared to Group-I ($p<0.05$). At two-minutes myoclonus was seen in 32 patients (64%) and 19 patients

(38%) respectively in Group-I and Group-II as shown in Table-3. Myoclonus was absent in 18 cases (36%) and 31 patients (62%) in Group-I and Group-II respectively. There was a statistically significant reduction in the incidence of myoclonus at two minutes in Group-II compared to Group-I ($p<0.05$). Figure 2 shows the reduction in the incidence of myoclonus in Group-II compared to Group-I at one and two minutes. Table-4 and Fig-3 depict the comparison of the grades of myoclonus seen at one minute in the two groups. Among the Group-I patients that showed presence of myoclonus, majority of them had grade-3 with 21 patients (42%) followed by eight patients (16%) showing grade-2 and five patients (10%) having Grade-1. Among the Group-II patients that had myoclonus, majority of them had grade-2 with six patients (12%) followed by Grade-3 with five patients (10%) and four patients (8%) showing grade-1. 16 patients (32%) had no myoclonus in Group-I and 35 patients (70%) in Group-II. Table-5 and Figure 4 show the comparison of the different grades of myoclonus seen at two minutes in the two groups. Group-I patients showing myoclonus, majority of them had grade-3 with 14 patients (28%) followed by 11 patients (22%) showing grade-2 and seven patients (14%) having Grade-1. Among the Group-II patients that had myoclonus, majority of them had grade-2 with seven patients (14%) followed by Grade-3 and Grade-1 with six patients (12%) each. 18 patients (36%) had no myoclonus in Group-I and 31 patients (62%) in Group-II.

DISCUSSION

Etomidate is a carboxylated imidazole widely used as intravenous anaesthetic induction agent. It confers the advantages of better haemodynamic stability, minimal respiratory depression and does not induce histamine release.¹³ However, the use of etomidate may be associated with undesirable effects such as myoclonus. The incidence of etomidate induced myoclonus in unmedicated patients is reported to be as high as 50% to 80%.^{7,14} The myoclonic movement is a bothersome problem¹⁴ and may also increase the risk of regurgitation and aspiration in non-fatal patients⁴ and hazardous in patients with open-globe injury.⁸ The evidence about pre-treatment with lidocaine to prevent etomidate induced myoclonus was relatively deficient when compared to the enormous amount of published literatures about interventions such as dexmedetomidine, midazolam and opioids. The present study demonstrated that intravenous lidocaine pre-treatment reduced the intensity and severity of etomidate induced myoclonus. Both the groups i.e., Group-I (Normal Saline) and Group-II (Lidocaine) are comparable with respect to their demographic profile such as age, weight, sex, ASA status, duration of anaesthesia and surgery. This was comparable with the study conducted Gupta P and Gupta M.⁸ In the present study, we found a statistically significant decrease in the incidence of etomidate induced myoclonus from 68% in Group-I (Normal Saline) to 30% in group-II (Lidocaine) at 1 minute ($p<0.05$). Similar to the present study regarding

the incidence of etomidate induced myoclonus at one minute (secondary outcome) Gupta P and Gupta M⁸ also reported a statistically significant decrease in the incidence of myoclonus from 60% with saline to 32% with lidocaine ($p=0.030$). A statistically significant decrease in the etomidate induced myoclonus incidence at two minutes (primary outcome) with the use of lidocaine (38%) compared with 64% in the saline group in the present study was comparable to the findings of Gupta P and Gupta M⁸ who reported a statistical significant reduction in the etomidate induced myoclonus from 76% in Group-I (Normal Saline) to 42% in group-II (Lidocaine) at 2 minutes ($p<0.05$). Singh KA et al⁴ also reported a significant decrease in the incidence of myoclonus from 76% (Normal Saline) to 44% (Lidocaine) with pre-treatment with lidocaine corroborating with the present study. Gultop F et al¹² studied the effect of pre-treatment with 2% lidocaine (1 ml) and saline, and observed that 56.6% incidence of myoclonus in the lidocaine group compared to 83% in the saline group which was comparable with the present study. Lang B et al¹⁵ also a series of randomized control trial (RCT) showing a reduction in the incidence of etomidate induced myoclonus i.e. 37.6% with lidocaine versus 73.6% with saline. Yang X et al¹⁶ also showed a reduction in the etomidate induced myoclonus in lidocaine group when compared with placebo. In the present study, the incidence of myoclonus at one and two minutes with 68% and 64% respectively in the control group and 30% and 38% respectively in the lidocaine group was observed which was in accordance with the findings of Luan HF et al¹⁷ who reported an incidence of etomidate induced myoclonus of 63.3% at one minute with normal saline. Lang B et al¹⁵ reported that there was a significant difference between the lidocaine group and the saline group in the incidence of etomidate induced mild myoclonus (13% with lidocaine versus 21.1% with saline) comparable with the present study. However, Gupta P and Gupta M⁸ reported no significant difference in the two groups. Gupta P and Gupta M⁸ reported a reduction in the incidence of moderate myoclonus with lidocaine pre-treatment compared to normal saline group (12% with lidocaine versus 18% with saline at one minute and 14% with lidocaine versus 22% with saline at two minutes) which was comparable with the present study. Lang B et al¹⁵ also documented a reduction in the incidence of etomidate induced moderate myoclonus with lidocaine pre-treatment compared to normal saline group (13.2% with lidocaine versus 28.2% with Normal Saline). Present study showed a significant reduction in the severity of etomidate induced myoclonus. Incidence of severe myoclonus at one minute decreased from 42% in normal saline group to 10% in the Lidocaine group. At two minutes the incidence of severe myoclonus decreased from 28% in normal saline group to 12% in the Lidocaine group. These findings corroborated with the studies done by Gupta P and Gupta M⁸ (32% in normal saline group versus 10% in the Lidocaine group at one minute and 42% in normal saline group versus 14% in the Lidocaine group at two minutes) and Lang B et al¹⁵ (24.3% in normal saline group versus 11.3% in the Lidocaine group). The involuntary myoclonic

movements seen with etomidate are believed to be caused by subcortical disinhibition.⁷ Disruption of the cortical GABA-mediated inhibition makes skeletal muscles susceptible to the spontaneous nerve transmissions, thereby leading to the myoclonic moments.¹⁰ The incidence of myoclonus has been shown to increase with the speed of etomidate administration and the period of observation.¹⁴ The property of Lidocaine to reduce the central nervous system excitability has been hypothesised as the mechanism behind its etomidate induced myoclonus suppressing action.¹² Lidocaine anticonvulsant mechanism of action of suppressing the cortically induced facilitation of motor neurons might also account at least partially for its myoclonus attenuating property.⁸ However, its supratherapeutic concentrations have been postulated to cause selective inhibition of cortical inhibitory pathways, the same mechanism proposed behind etomidate induced myoclonus.¹⁸ In our study lidocaine was administered 2 minutes before etomidate to justify its time to onset of action (45-90 seconds). An observation period of two minutes after etomidate injection was chosen in the present study to capture the true incidence of myoclonus in both the groups. The majority of myoclonic episodes occur within two minutes of etomidate administration and approximately 50% of the episodes occur after the first minutes as reported by Sidighinejad A et al.¹⁰

In majority of the patients in both the study groups of the present study, myoclonus occurred within two minutes after the start of induction as also reported by Mullick P et al.¹⁹ The period of observation for myoclonus varied from one to three minutes in most previous studies suggesting that the actual incidence of etomidate induced myoclonus 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 myoclonus, further studies are needed to identify the optimal observation period. The main limitation of our study is that we used only a single dose (1 mg/Kg) of lidocaine. A dose response decrease in the incidence of myoclonus has been established with increasing doses of lidocaine by previous author.⁸ Therefore, through the present study, we sought to establish the effect of the most commonly employed dose, that is 1 mg/Kg of lidocaine on etomidate induced myoclonus.

Variables	Group I (Normal Saline)	Group II (Lidocaine)	p
Age, years (Mean $\pm$ SD)	39.02 $\pm$ 10.21	39.4 $\pm$ 12.4	0.868 (NS)
Sex (M: F)	40:10	36:14	0.354 (NS)
Weight in Kg (Mean $\pm$ SD)	57.9 $\pm$ 10.1	57.87 $\pm$ 9.1	0.988 (NS)
ASA (I: II)	46:04	47:03	0.699 (NS)

Table 1. Demographic Characteristics

NS – Not significant; ASA – American Society of Anesthesiologists; SD – Standard deviation

Myoclonus at One Minute	Group I (Normal Saline)	Group II (Lidocaine)	p
	Number	Number	%
Absent	16	35	70
Present	34	15	30
Total	50	50	

Table 2. Comparison of Incidence of Myoclonus at One Minute

Myoclonus at Two Minutes	Group I (Normal Saline)		Group II (Lidocaine)		p
	Number	(%)	Number	%	
	Absent	18	36	31	62
Present	32	64	19	38	
Total	50		50		

Table 3. Comparison of Incidence of Myoclonus at Two Minutes

Table 3. Comparison of Incidence of Myoclonus at Two Minutes

Myoclonus Intensity	Group I (Normal Saline)		Group II (Lidocaine)		p
	Number	(%)	Number	(%)	
Grade-0	16	32	35	70	0.001
Grade-1	05	10	04	08	
Grade-2	08	16	06	12	
Grade-3	21	42	05	10	
Total	50		50		

Table 4. Comparison of Grades of Myoclonus at One Minute in Both the Groups

Myoclonus Intensity	Group I (Normal Saline)		Group II (Lidocaine)		p
	Number	%	Number	%	
Grade-0	18	36	31	62	0.005
Grade-1	07	14	06	12	
Grade-2	11	22	07	14	
Grade-3	14	28	06	12	
Total	50		50		

Table 5. Comparison of Grades of Myoclonus at Two Minutes in Both the Groups

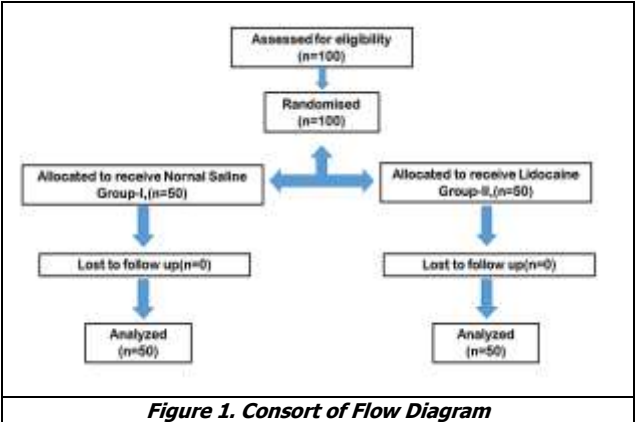


Figure 1. Consort of Flow Diagram

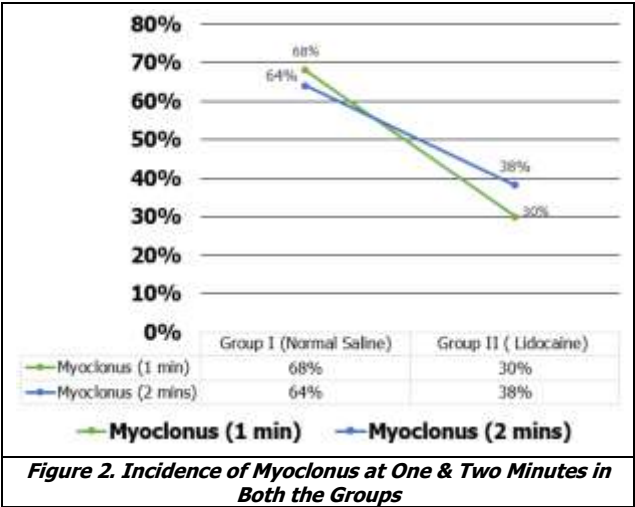


Figure 2. Incidence of Myoclonus at One & Two Minutes in Both the Groups

Establishing a dose response relationship between etomidate induced myoclonus and varying doses of lidocaine after establishing a drug-response relationship as demonstrated by our study is a way forward.

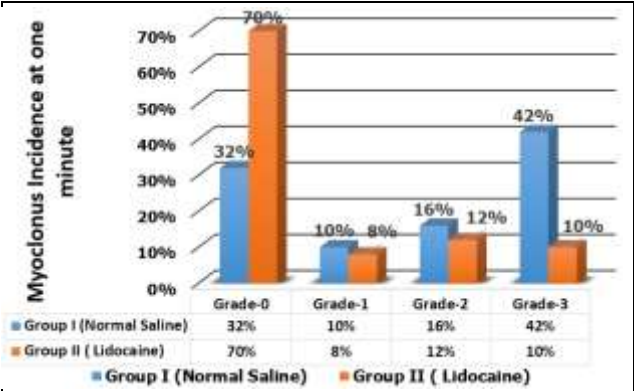


Figure 3. Comparison of Grades of Myoclonus at One Minute in Both the Groups

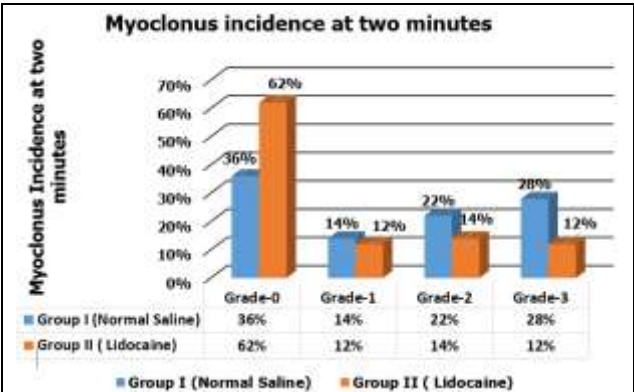


Figure 4

CONCLUSIONS

Pre-treatment of lidocaine could serve as one effective approach to decrease both the incidence and the severity of etomidate-induced myoclonus, with limited influence on the hemodynamic stability of patients. Lidocaine may be recommended as premedication to reduce the etomidate-induced myoclonus without significant side effects. However, more evidence with high quality data and a larger sample size is necessary to determine the preferred pharmacological option and the proper prophylactic dosage of lidocaine. It remains an open question for further study.

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