Original Article

Comparison of different doses of intravenous lignocaine on etomidate-induced myoclonus: A prospective randomised and placebo-controlled study

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ABSTRACT

Background and Aims: Etomidate-induced myoclonus (EM) is observed in 50%–80% of unpremedicated patients. Low-dose lignocaine has been shown to attenuate but not abolish the EM. The aim of this prospective, randomised controlled study was to compare the different doses of lignocaine on the incidence and severity of EM. **Methods:** Two hundred adult patients were randomly assigned into four groups to receive saline placebo (Group I) or IV lignocaine 0.5 mg/kg (Group II), 1 mg/kg (Group III) or 1.5 mg/kg (Group IV) 2 min before injection etomidate 0.3 mg/kg IV. The patients were assessed for the EM using a four-point intensity scoring system. Our primary outcome was the incidence of myoclonus at 2 min (EM2). The incidence of myoclonus at 1 min (EM1) and severity of myoclonus constituted the secondary outcomes. ANOVA and Pearson Chi-square test were used for statistical analysis and $P < 0.05$ was considered as statistically significant. **Results:** The incidence of EM was significantly reduced in Groups III [(EM1: 32% vs. 60%, $P = 0.009$); (EM2: 42% vs. 76%, $P = 0.001$)] and IV (EM2: 54% vs. 76%, $P = 0.035$) compared with Group I. Lignocaine 1 mg/kg and 1.5 mg/kg significantly reduced the incidence of severe myoclonus at 2 min (14% each) compared to Groups I (42%, $P = 0.003$) and II (32%, $P = 0.032$). **Conclusion:** Lignocaine 1 mg/kg and 1.5 mg/kg IV pretreatment significantly reduces the incidence of EM, with maximum attenuation observed with 1 mg/kg.

Key words: Anaesthesia, etomidate, lidocaine, myoclonus, premedication

INTRODUCTION

Etomidate, a carboxylated imidazole, confers the advantages of better haemodynamic stability and less injection pain compared to propofol; when used for the induction of general anaesthesia.[1] However, etomidate-induced myoclonus (EM), seen in 50%–80% of unpremedicated patients, jeopardises its use.[1,2] EM may vary from innocuous movements at finger to intense clonic movements. These involuntary movements may lead to muscle damage, myalgia, hyperkalaemia, accidental dislodgement of the vascular access and monitoring devices.[3] The EM may prove to be particularly hazardous in patients with open-globe injury, full stomach, hypertension, coronary artery disease and intracranial aneurysms.[2-4] A number of drugs such as opioids, benzodiazepines, α_2 agonists, N-methyl-D-aspartate antagonists, muscle relaxants and lignocaine in low doses (20 mg) have been found to attenuate but not completely abolish the EM.[2-5] Lignocaine in higher doses (1.5 mg/kg) is commonly employed preoperatively to blunt the sympathetic response to laryngoscopy and intubation. There is, however, no study evaluating the dose-response relationship between different doses of IV lignocaine

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and the incidence of EM. The present study was therefore conducted with the aim to compare the effect of three weight-based doses of intravenous (IV) lignocaine (0.5, 1 and 1.5 mg/kg) on the incidence of EM.

METHODS

This prospective, randomised, double-blind and placebo-controlled study was conducted after obtaining approval from the institutional ethics committee. The ethical principles of medical research involving human patients as specified in the declaration of Helsinki were strictly adhered to while conducting this trial. After obtaining written informed consent, 200 patients of either sex belonging to 20–60 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, 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, sedatives or chronic opioid therapy were excluded from the study. None of the patients received any premedication.

After arrival in the operation theatre, monitoring such as electrocardiograph, pulse oximeter and non-invasive blood pressure (Datex-Ohmeda, cardiocap/5, GE Healthcare, Helsinki, Finland multichannel monitor) were attached to the patient and baseline vitals recorded. A 20G IV cannula was secured into a vein on the dorsum of the hand and attached to a Ringer lactate drip. Depending on the drug used as IV premedication, the patients were randomised using computer generated random number list into one of the following four equal groups (n = 50): Group I: 6 mL of normal saline (NS), Group II: 0.5 mg/kg of lignocaine (Loxicard® 2%, Neon, Mumbai, India) diluted to 6 mL (with NS), Group III: 1 mg/kg lignocaine diluted to 6 mL (with NS) or Group IV: 1.5 mg/kg lignocaine diluted to 6 mL (with NS). The premedication drug was prepared in identical 10 mL syringes labelled as the 'study drug' outside the operation theatre by an independent anaesthesiologist not involved further in the study. All the study drugs were prepared to an accuracy of 1 mg using an insulin syringe and finally diluted to 6 mL. The anaesthesiologists administrating the study drug and monitoring for the myoclonus and the patients were unaware of the group allocation. Two minutes after administering the study drug, etomidate (Hypnodate®, Neon) 0.3 mg/kg IV was administered over 30 s and the patients were monitored for myoclonus over the next 2 min. After induction of anaesthesia, the patients' lungs were ventilated with 100% oxygen using an appropriate-sized face mask. Myoclonus was defined as 'involuntary short muscle contractions leading to short observable movements in parts of body' and its severity assessed using the four-point intensity scoring (0): No myoclonus; (1): Mild myoclonus (mild movements of a body segment, e.g., finger or a wrist only); (2): Moderate myoclonus (mild movements of two different muscles e.g., face and leg); and (3): Severe myoclonus (intense tonic movements in two or more muscle groups e.g., fast adduction of a limb).[2] Depending on the time of onset, the presence or absence of myoclonus at 1 min (EM1) and 2 min (EM2) was recorded. Fentanyl 2 μg/kg IV and vecuronium bromide 0.1 mg/kg IV were administered after the 2 min observation period or the onset of myoclonus, whichever was earlier and mask ventilation continued with nitrous oxide and isoflurane in oxygen for another 3 min. Tracheal intubation with an appropriate-sized endotracheal tube was performed after 3 min and anaesthesia maintained with nitrous oxide and isoflurane in oxygen. The patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 35–40 mm Hg.

The primary outcome variable for the study was the incidence of myoclonus at 2 min. The incidence of myoclonus at 1 min and the severity of myoclonus were the secondary outcome variables for the study.

Assuming the incidence of EM2 to be 80% in the control group and a reduction in incidence in the treatment group by 30% as clinically significant, a sample size of 50 patients per group was estimated with α =0.05 and power = 80%. As it was an intraoperative study with no expected loss to follow-up, we decided to include 200 patients in the study.

The data were tabulated in MS Excel 2010 and statistical analysis performed using SPSS 19.0 for Windows (Statistical Package for Social Sciences, Chicago, IL, USA). The continuous data such as the patient's age and weight are expressed as

mean ± standard deviation, whereas the categorical data, such as sex, ASA physical status, type of surgery and the incidence of myoclonus, expressed as frequencies (percentages). The data were analysed using one-way analysis of variance ANOVA and Pearson Chi-square test for continuous and categorical variables, respectively. $P < 0.05$ was considered as statistically significant.

RESULTS

Out of the 226 consecutive patients assessed for eligibility, 200 met the inclusion criteria and were included in the study. These 200 patients were randomised into four groups of 50 patients each [Figure 1]. Demographic characteristics (age, weight, sex and ASA physical status) were similar across the treatment groups [Table 1]. Lignocaine pretreatment significantly reduced the incidence of both EM1 ($P = 0.030$) and EM2 ($P = 0.006$) [Figure 2]. However, the individual group-to-group analysis demonstrated a statistically significant reduction in the incidence of EM2 (primary outcome) between Groups I and III (76% vs. 42%, relative risk [RR] = 0.503, 95% confidence interval [CI] = 0.339–0.747, $P = 0.001$) and Groups I and IV (76% vs. 54%, RR = 0.632, 95% CI = 0.435–0.919, $P = 0.035$) only. Similarly, a statistically significant reduction in the incidence of EM1 was observed between Groups I and III (60% vs. 32%, RR = 0.552, 95% CI = 0.354–0.862, $P = 0.009$). Although the incidence of both EM1 and EM2 was higher in Groups I versus II (EM1: 60% vs. 50%, $P = 0.422$; EM2: 76% vs. 60%, $P = 0.133$) and III versus IV (EM1: 40% vs. 32%, $P = 0.532$; EM2: 54% vs. 42%; $P = 0.608$); the results failed to reach statistical significance.

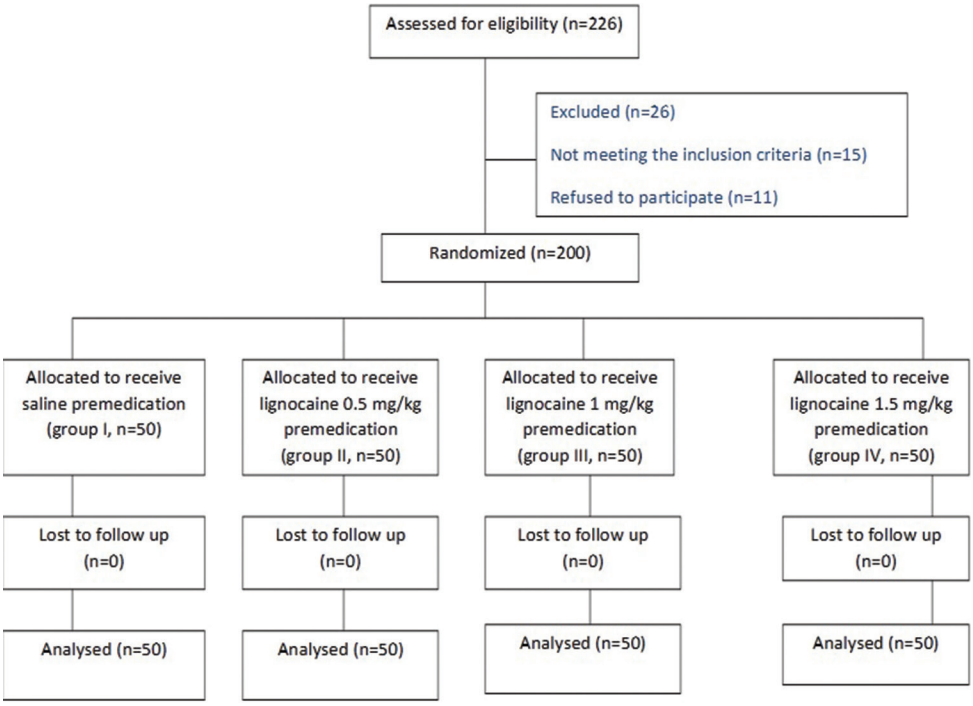


Figure 1: Consort flow diagram

Table 1: Demographic characteristics

Variable	Group I (*n*=50)	Group II (*n*=50)	Group III (*n*=50)	Group IV (*n*=50)	*P*
Age, years (mean±SD)	40.2±11.796	39.12±11.52	38.74±13.05	38.98±12.43	0.936 (NS)
Gender, *n* (%)					
Female	31 (62)	31 (62)	28 (56)	29 (58)	0.905 (NS)
Male	19 (38)	19 (38)	22 (44)	21 (42)	
Weight, kg (mean±SD)	59.38±7.98	57.96±10.97	60.40±8.08	59.09±9.26	0.591 (NS)
ASA, *n* (%)					
I	36 (72)	36 (72)	35 (70)	37 (74)	0.978 (NS)
II	14 (28)	14 (28)	15 (30)	13 (26)	

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

Figures 3 and 4 depict the severity grading of myoclonus observed at 1 and 2 min, respectively. A statistically significant reduction in the incidence of severe myoclonus at 1 min was observed between Groups I and III (RR = 0.418, 95% CI: 0.190–0.920, P = 0.013); Groups I and IV (RR = 0.418, 95% CI: 0.190–0.920, P = 0.013); Groups II and III (RR = 0.474, 95% CI: 0.218–1.030, P = 0.040) and Groups II and IV (RR = 0.474, 95% CI: 0.218–1.030, P = 0.040). Similarly, statistically significant reduction in the incidence of severe myoclonus at 2 min was observed between Groups I and III (RR = 0.419, 95% CI: 0.214-0.817, P = 0.003); Groups I and IV (RR = 0.419, 95% CI: 0.214–0.817, P = 0.003); Groups II and III (RR: 0.545, 95% CI: 0.285–1.043, P = 0.032) and Groups II and IV (RR: 0.545, 95% CI: 0.285–1.043, P = 0.032). The incidence of severe myoclonus was similar between Groups III and IV at both 1 min and 2 min.

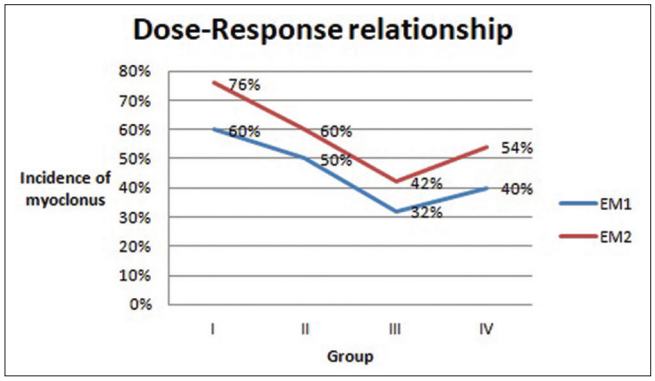
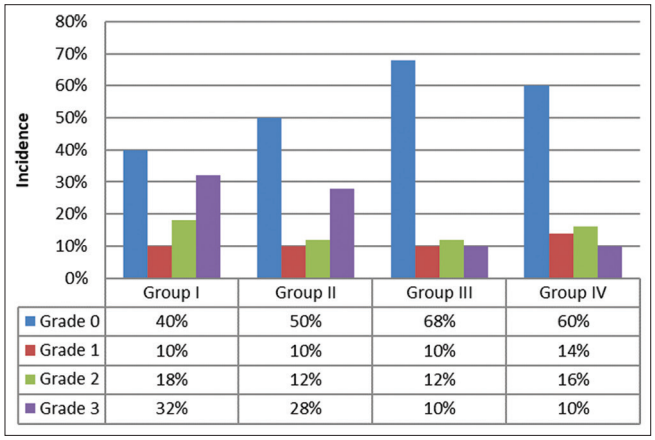
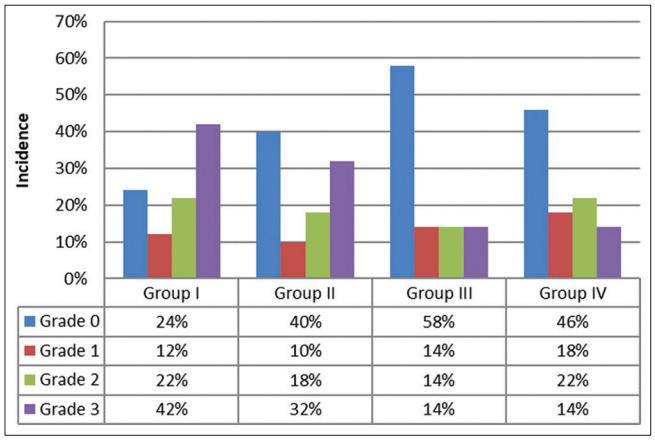


Figure 2: Dose (lignocaine)-response (incidence of myoclonus) relationship



	Group I	Group II	Group III	Group IV
Grade 0	40%	50%	68%	60%
Grade 1	10%	10%	10%	14%
Grade 2	18%	12%	12%	16%
Grade 3	32%	28%	10%	10%

Figure 3: Severity of etomidate-induced myoclonus at 1 min in four groups



	Group I	Group II	Group III	Group IV
Grade 0	24%	40%	58%	46%
Grade 1	12%	10%	14%	18%
Grade 2	22%	18%	14%	22%
Grade 3	42%	32%	14%	14%

Figure 4: Severity of etomidate-induced myoclonus at 2 min in four groups

DISCUSSION

Our study results demonstrated that IV lignocaine pretreatment reduced the intensity and severity of EM; a statistically significant reduction was, however, observed with only 1 mg/kg and 1.5 mg/kg. Lignocaine comes close to being an ideal pretreatment for the attenuation of EM in that it has a rapid onset, short duration of action, minimal cardio-respiratory depression and does not prolong recovery from anaesthesia in the clinically used doses.[6] The literature evaluating the efficacy of lignocaine against EM is scarce; with the published literature evaluating only low doses of lignocaine (20 mg, <0.5 mg/kg).[5,6] Lignocaine 20 mg (<0.5 mg/kg) IV has been demonstrated to significantly reduce the incidence of EM1 from 83% to 56%.[5] Lignocaine 20 mg IV premedication was found to significantly reduce the incidence of EM1 from 76% to 44% in an another study.[6] We found a similar incidence of EM1 in Group II of 50%; the difference, however, failed to reach statistical significance. This might be due to differences in the demographic profile (explaining the higher incidence in the control group), the study protocol (speed of etomidate administration, time interval between lignocaine premedication and etomidate administration), small sample size and the different myoclonus severity scoring scale used in the previously reported studies.[5,6] A weight-based dosing strategy (mg/kg body weight) is scientifically more valid, commonly employed clinically and is superior or at least non-inferior to the fixed-dose regimen. The same holds true for IV lignocaine as well, for the majority of the clinical indications, as is evident from the published literature and recommendations.[7-9] We, therefore, sought to answer the clinical question in context using different-weight adjusted doses of IV lignocaine. The incidence of EM has been shown to increase with the speed of etomidate administration and the period of observation.[10] We therefore

employed a standard protocol to minimise these confounding variables. The reported incidence of myoclonus with etomidate injection over 30 s and observation period of 1 min has been found to vary widely.[11,12] The incidence of myoclonus and severe myoclonus at 1 min of 60% and 32%, respectively, in the control group, as observed in the present study, is in accordance with that observed by the other authors.[11] The speed of etomidate injection was not mentioned in an earlier study evaluating the effect of lignocaine on EM.[6] Lignocaine was administered 2 min before etomidate to justify its time to onset of action (45-90 s). The majority of the myoclonic episodes occur within 2 min of etomidate administration and approximately 50% of the episodes occur after the 1st min.[13] An observation period of 2 min was therefore chosen to capture the true incidence of myoclonus both in the unpremedicated and the premedicated groups. Only lignocaine 1 mg/kg was found to reduce the incidence of EM1 significantly.

A number of hypotheses have linked EM either to a seizure-like activity or disinhibition phenomenon with earlier suppression of the cortical before subcortical activity.[5,14,15] Disruption of the cortical GABA-mediated inhibition makes skeletal muscles susceptible to the spontaneous nerve transmissions, thereby leading to the myoclonic movements.[13] Lignocaine propensity to reduce the central nervous system excitability has been hypothesised as the mechanism behind its EM suppressing action.[5] The mechanism behind EM has also been postulated to be similar to convulsive seizures.[3,14,15] Lignocaine anticonvulsant mechanism of action of suppressing the cortically induced facilitation of motor neurons might also account at least partially for its myoclonus attenuating property. However, its supratherapeutic concentrations have been postulated to cause selective inhibition of cortical inhibitory pathways, the same mechanism proposed behind EM.[16] This might explain the therapeutic plateau effect seen on the dose-response (incidence of EM) curve for lignocaine seen at doses higher than 1 mg/kg; as observed in our study [Figure 2].

Our study has a few limitations. First, our study population, i.e., ASA I/II patients does not represent the ideal population in which etomidate is used as the induction agent of choice. Validating our results in those with haemodynamic or cardiovascular instability is definitely a step forward. Second, we selected only three weight-based doses of IV lignocaine. A dose-response study should ideally employ sequentially increasing doses of a drug (IV Lignocaine). Future studies elucidating the effect of other doses of IV lignocaine on EM are therefore warranted.

CONCLUSION

Lignocaine 1 mg/kg and 1.5 mg/kg IV pretreatment significantly reduce the incidence of etomidate-induced myoclonus at 2 min, with maximum attenuation observed with 1 mg/kg. Premedication with lignocaine 1 mg/kg IV significantly reduces the incidence of EM at 1 min. Both doses (1 mg/kg and 1.5 mg/kg) of IV lignocaine are equally effective in reducing the incidence of severe grade three myoclonus.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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