DOI: 10.7860/JCDR/2023/60034.17439

Original Article

Anaesthesia Section

Dexmedetomidine versus Lignocaine in the Prevention of Etomidate-induced Myoclonus-A Randomised Double-blinded Study

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ABSTRACT

Introduction: Etomidate is a preferred induction agent owing to its stable haemodynamic profile, minimal respiratory side-effects, minimal histamine release, cerebral protection and its property of rapid onset and short duration. However, myoclonus has been reported as one of its side-effects which poses great concern. Amongst the various drugs used to attenuate it, the role of intravenous (i.v.) Dexmeditomidine and Lignocaine have been reported in literature to be of great success.

Aim: To compare the efficacy of Dexmedetomidine and Lignocaine in preventing Etomidate-induced Myoclonus.

Materials and Methods: The randomised, double-blinded study included 104 adult consented patients, of either sex, American Society of Anaesthesiology (ASA) I and II, aged 18-65 years, undergoing routine surgery under general anaesthesia. They were randomly allocated into two groups of 52 patients each viz., Group I receiving 0.5 µg/kg of injection (inj.) Dexmedetomidine i.v. and Group II 1 mg/kg of inj. Lignocaine diluted in 10 mL normal saline i.v. The incidence and severity of myoclonus were assessed and recorded within 90 seconds after etomidate injection using a four point severity scale. The collected data were entered in Statistical Package for Social Sciences (SPSS) version 21.0.

Results: Total 104 subjects with the demographic parameters such as age, sex, ASA and weight comparable between the two groups were analysed. Group I recorded lesser number of patients (17, 32.7%) to myoclonus as compared with Group II (21, 40.4%), (p-value=0.41). Maximum patients in Group I developed grade I myoclonus while in Group II, it was grade 2. No patients in Group I developed grade 3 myoclonus as against 5 patients in Group II (p-value=0.03).

Conclusion: Dexmedetomidine and Lignocaine were equally effective in the prevention of Etomidate-induced myoclonus but dexmeditomedine was better because of lesser incidence of severe grade myoclonus.

Keywords: Efficacy, Four point severity scale, Incidence and severity, Induction agent

INTRODUCTION

Etomidate has been a favourite induction agent among anaesthesiologists, owing to its distinct attractive pharmacologic attributes, viz., rapid onset of profound hypnosis [1], brevity of action [2], lack of cardiovascular depression [3] and consequent better haemodynamic profile [4], minimal respiratory side-effects [5], minimal histamine release [6,7] and protection of intracranial pressure [7]. Its lack of effect on the sympathetic nervous system, baroreceptor reflex regulatory system and its effect of increased coronary perfusion even on patients with moderate cardiac dysfunction makes it an induction agent of choice in cardiac disease patients [4]. The side-effects such as pain on injection, superficial thrombophlebitis and haemolysis, were resolved after hyperosmolar etomidate emulsion with propylene glycol was substituted for water soluble solution [6,8] and of adrenocortical suppression by synthesis of rapidly metabolised soft analogues [9].

However, myoclonus continues to be a clinical problem, with an incidence of 50-80% in non premedicated patients [6,10], can lead to muscle fibre damage, myalgia, hyperkalemia, accidental dislodgement of vascular access and monitoring devices [11]. The consequences of etomidate-induced myoclonus is temporary in most patients, however it can cause regurgitation and aspiration in non fasted emergency patients, prolapse of vitreous material in patients with open globe injuries and increase myocardial oxygen consumption in patients with limited cardiovascular reserve [6,10].

A wide variety of drugs were being investigated for their ability to suppress these myoclonic movements like $\alpha 2$ agonists (dexmedetomidine) [10,12-15], benzodiazepines [6,12,15-18], lidocaine [9,11,17], N-methyl-D-aspartate (NMDA) antagonists (magnesium sulfate) [6], steroids (dexamethasone) [19] at the cost of their own side-effects. An ideal drug for preventing myoclonus should be short acting, have minimal effects on respiration and haemodynamics and do not prolong recovery from anaesthesia.

Dexmedetomidine, a highly selective $\alpha 2$ agonist, with anxiolytic, sedative and analgesic properties, can cause sympatholysis with anaesthetic sparing effects. Some studies have evaluated its efficacy in reducing the incidence of etomidate induced myoclonus [10,12-15] with promising results. Though, it attenuated myoclonus in different doses (0.5-1) µg/kg, its dose of 0.5 µg/kg was found to be better than its higher doses, due to fewer side-effects like sedation and respiratory depression [16].

Lignocaine, due to its propensity to reduce central nervous system excitability [11], was also found to be effective in the attenuation of myoclonus in studies with different doses [9,11,17] and the dose of 1 mg/kg seems to the most effective [11]. With this background, the study aimed to compare the effect of Dexmedetomidine and Lignocaine on the incidence of Etomidate induced myoclonus, at the doses of 0.5 µg/kg and 1 mg/kg respectively. The primary outcome was to compare the incidence and severity of Etomidate induced myoclonus in the two groups. The secondary measure was to determine other associated side-effects for the same.

MATERIALS AND METHODS

This randomised, double-blinded clinical trial was conducted in the Department of Anaesthesiology, Regional Institute of Medical sciences, a tertiary care centre, at Imphal, Manipur, India, from October 2019 to September 2021. The trial was conducted after getting approval from the Institutional Research Ethics Board (IREB)

vide order no. A/206/REB-Comm(SP)/RIMS/2015/523/1/2019, dated 24th October 2019. The trial was also registered at the Clinical Trials Registry- India (CTRI) bearing no CTRI/2021/06/034499 before the commencement of the study. Informed written consent were also taken from the patients concerned. All patients undergoing routine upper abdominal surgery (cholecystectomy-both open and laparoscopic) under general anaesthesia fulfilling the inclusion criteria were enrolled.

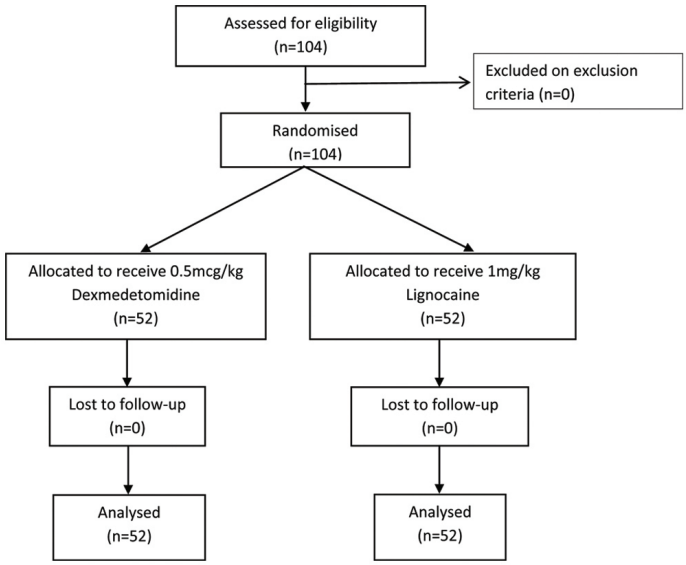
Sample size calculation: Sample size was calculated based on the study by Gupta P and Gupta M, where the incidence of etomidate-induced myoclonus was 32% and 60% in the lignocaine and control groups, respectively [11]. Considering, α-value of 0.05 and β-power of 80%, 52 patients were recruited for each groups allowing 5% dropout rate.

Inclusion criteria: Patients in the age group of 18-65 years, American Society of Anaesthesiologist (ASA) grade I and II of both sex undergoing routine upper abdominal surgery under general anaesthesia were enrolled for the study.

Exclusion criteria: Patients with history of allergy to study drugs (etomidate, dexmedetomidine, lignocaine), diabetes, hypertension, cardiovascular, respiratory or neurologic disease, adrenocortical dysfunction and patients with morbid obesity were excluded from the study. Anticipated difficult intubation patient were also excluded from the clinical trial.

Study Procedure

The participants were randomly allocated, using a computer-generated list of random numbers, into one of the two groups (n=52). Group I received 0.5 µg/kg of Inj. Dexmedetomidine in 10 mL normal saline i.v. and Group II received 1 mg/kg of 2% preservative free Inj. Lignocaine diluted in 10 mL normal saline i.v. The drugs were prepared by another anaesthesiologist not involved further in the study, in identical 10 mL syringes labelled as the "study drug" outside the operation theatre. The principal investigator, who was blinded to the group allocation, administered the drug to the patients, who were also unaware of the drug he/she received [Table/Fig-1].



[Table/Fig-1]: CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Methods: Patients were secured with a 20G i.v. cannula into a vein on the dorsum of the patient's non dominant hand and attached to a ringer lactate drip in the preanaesthetic room. On arrival to the operation theatre, all the patients were preoxygenated with 100% oxygen via face mask and the study drug was administered as pretreatment over 5 minutes, depending on the randomly allocated group. As the incidence of myoclonus induced by etomidate depends on the dosage and speed of injection, it was administered in the same injection rate and dosage to all [6,20]. Two minutes after administering the study drug, etomidate 0.3 mg/kg i.v. was administered over 30 seconds and the patients were monitored for myoclonus over the next 90 seconds, and its severity was assessed using the four-point intensity scoring [11]. Induction of anaesthesia was achieved with etomidate and the study was considered complete at this point and further anaesthesia technique was not influenced by this study. Fentanyl 2 µg/kg i.v. and Rocuronium 0.6 mg/kg i.v. were administered after the 90 seconds observation period or the onset of myoclonus, whichever was earlier as anticipated difficult intubation patient were excluded from the study. Tracheal intubation with an appropriate-sized endotracheal tube was performed after three minutes 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. Myoclonic movements within 90 seconds were observed after the completion of etomidate injection.

The independent study variables such as age, sex, weight, ASA, duration and types of surgery and dependent variables like the incidence of myoclonus were recorded for both the groups. Myoclonus was assessed using four-point intensity scoring for assessment of myoclonus after Etomidate injection [11] as

- Score 0-absent,
- Score-1 with mild movements of a body segment (e.g., finger or a wrist only),
- Score-2 with mild movements of 2 different muscles (e.g., face and leg)
- Score 3- with intense tonic movements in 2 or more muscle groups (e.g., fast adduction of a limb).

STATISTICAL ANALYSIS

The collected data were entered in Statistical Package for Social Sciences (SPSS), Chicago, IL, USA version 21.0 for Windows. Data analysis was carried out by another independent researcher who was not involved in any stages of the procedure. The data were analysed using independent t-test and Pearson Chi-square test for continuous and categorical variables, respectively. The p-value <0.05 was considered as statistically significant.

RESULTS

A total of 104 patients completed the study. The demographic parameters between the two groups were comparable (p-value >0.05) and did not affect the study outcome, as shown in [Table/Fig-2]. The duration and type of surgery were also comparable (p-value >0.05).

Parameters	Group I (Dexmedetomidine)	Group II (Lignocaine)	p-value
Age (in years) Mean±SD	35.52±11.73	36.63±11.49	0.62
Weight (in kg) Mean±SD	59.70±8.92	62.85±8.03	0.31
Sex Male:Female	15:37	22:30	0.15
ASA I:II	48:4	49:3	0.69
Type of surgery Laparoscopic: Open Cholecystectomy	39:13	41:11	0.64
Duration of surgery (in mins) Mean±SD	55.21±7.39	57.25±6.84	0.14

[Table/Fig-2]: Demographic parameters.
p-value <0.05 is significant

Group I recorded lesser number of patients (17, 32.7%) with myoclonus as compared with Group II (21, 40.4%), even though the difference was not statistically significant (p-value=0.41). Assessment of severity showed that maximum patients in Group I developed grade I myoclonus while in Group II, it was grade 2.

No patients in Group I developed grade 3 myoclonus as against 5 patients in Group II and the difference is statistically significant (p-value=0.03) [Table/Fig-3]. There were no incidence of side-effects such as abnormal Electrocardiography (ECG) changes such as bradycardia, arrhythmias, etc., haemodynamic instability, Central Nervous System (CNS) effects in the two groups.

Severity of myoclonus	Group I (Dexmedetomidine)	Group II (Lignocaine)	Total	p-value
Grade 0 (Absent myoclonus)	35 (67.3%)	31 (59.6%)	66 (63.5%)	-
Myoclonus present	17 (32.7%)	21 (40.4%)	38 (36.5%)	0.41
Grade 1	13 (25%)	7 (13.5%)	20 (19.2%)	**0.03**
Grade 2	4 (7.7%)	9 (17.3%)	13 (12.5%)	
Grade 3	0	5 (9.6%)	5 (4.8%)	

[Table/Fig-3]: Incidence and severity of myoclonus.
p-value <0.05 is significant

DISCUSSION

An ideal drug for preventing myoclonus should be short acting, have minimal effects on respiration and does not prolong recovery from anaesthesia [21]. The present study evaluated the efficacy of dexmedetomidine and lignocaine in attenuating etomidate-induced myoclonus. Luan HF et al., compared two different doses of dexmedetomidine, namely 0.5 µg/kg and 1 µg/kg, in preventing myoclonic movements caused by etomidate, which showed that at both the doses, myoclonus was significantly reduced [10]. However, the incidence of hypotension and severe bradycardia (Heart Rate (HR) <50 beats per minute) was more at the dose of 1 µg/kg and recommended the dose of 0.5 µg/kg, due to its fewer side-effects. Hence, dexmedetomidine in the dose of 0.5 µg/kg was used for this study.

Gupta P and Gupta M subjected three different doses 0.5 mg/kg, 1 mg/kg and 1.5 mg/kg of lignocaine to compare their effects in attenuating etomidate-induced myoclonus, which showed statistically significant reduction with the latter two doses, out of which the maximum reduction was with the dose of 1 mg/kg [11]. Therefore, the study chose to employ lignocaine in the dose of 1 mg/kg. Do SH et al., showed that the incidence of myoclonus induced by etomidate depends on the dosage and speed of injection, with a slow rate of injection reducing its incidence and severity [20]. Hence, etomidate was administrated in the same injection rate (over 30 seconds) and dosage (0.3 µg/kg) to the study groups.

The demographic profile in terms of age, gender, ASA status and weight was found to be statistically not significant between the two study groups and were comparable to that of the study by Gupta P and Gupta M [11]. The present study, recorded 32.7% incidence of myoclonus in Group I (Dexmedetomidine) while it was 40.4% in Group II (Lignocaine) and difference was found to be statistically insignificant (p-value=0.415). These observations were corroborating with a handful of studies using dexmedetomidine in the dose of 0.5 µg/kg such as those of Luan HF et al., (30%), Patel MH et al., (33.3%) and Gunes Y et al., (30%) [10,12,13]. However, the studies by Dey S and Kumar M, and Ghodki PS and Shetye NN, reported higher incidence of myoclonus in the dexmedetomidine group (45%) [15,22]. The difference might be attributed to the longer observation period of 5 minutes in both these studies, in contrast to 90 seconds in the present study.

Gupta P and Gupta M reported the incidence of myoclonus as 42% at the end of 2 minutes in the dose of 1 mg/kg, a finding which was shared by the present study (40.4%) [11]. The observation with lignocaine Group I in the present study also corroborated with that reported by Rajkumari R et al., who proved that lignocaine was efficacious in preventing myoclonus and found an incidence of 38% at the dose of 1 mg/kg of lignocaine after 2 minutes of observation [23]. The lower incidence of 30% at 1 minute in the same study might have been due to the shorter period of observation. The present study findings were also shared by those of Singhal S and Gupta R, who reported an incidence of myoclonus at 40% with 1 mg/kg of lignocaine and of Jyoti B et al., who found an incidence of 40.6% with a fixed dose of 60 mg of i.v. lignocaine after 90 seconds of observation [24,25].

Regarding the severity of myoclonus, the present study proved similar to many previous studies. The incidence of mild, moderate and severe grades (grades 1, 2 and 3) of myoclonus were 25%, 7.7% and 0%, respectively in the dexmedetomidine group (Group I) while it was 13.5%, 17.3% and 9.6%, respectively in the lignocaine group (Group II). This difference was found to be statistically significant (p=0.03). Gunes Y et al., reported the incidence of mild, moderate and severe myoclonus as 22%, 8% and 0% with 1µg/kg of dexmedetomidine, which were similar to the findings of the present study [13]. Other comparable studies included those of Patel MH et al., (23.3%, 10% and 0%) and Isitemiz I et al., (30%, 6.7% and 0%) with similar incidence of mild, moderate and severe myoclonus [12,16].

Gupta P and Gupta M found 14%, 16% and 10% incidence of mild, moderate and severe myoclonus respectively with 1.5 mg/kg of lignocaine, similar to the observations in the group of patients who received lignocaine (Group II) in the present study [11]. The findings by Rajkumari R et al., of 12%, 14% and 12% incidence of mild, moderate and severe myoclonus respectively with 1 mg/kg of lignocaine and 15%, 20% and 10% incidence with 0.5 mg/kg of lignocaine observed in the study by Singhal S and Gupta R, also corroborated with the present study [23,24]. Severe myoclonus was not uncommon in most of the studies which used lignocaine (Group II), which was observed in the present study also.

Limitation(s)

Firstly, the study was a single centre research and study sample was not representative of the ideal population. Secondly, neither the duration of myoclonus was included in the present study, which was as relevant as the incidence and severity of the same, nor an electromyograph recording was employed. Thirdly, the chosen time period of observation was based on the previous studies which was usually 1-3 minutes and the actual incidence of myoclonus can be higher than reported. Hence, a consensus on an optimal observation period is warranted in further studies. Lastly, the study employed only one particular dose of each of these drugs and hence studies evaluating their optimal doses with maximum efficacy and least side-effect profile are needed.

CONCLUSION(S)

Dexmedetomidine and Lignocaine were both effective in the prevention of Etomidate-induced myoclonus even though Dexmedetomidine had got slight upper edge in term of severity of pain. However, comparing these two drugs was unprecedented and hence future studies employing this combination are imperative to acquire more evidence with high quality data.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 25, 2022
- Manual Googling: Nov 02, 2022
- iThenticate Software: Nov 28, 2022 (12%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 03, 2022**
Date of Peer Review: **Oct 19, 2022**
Date of Acceptance: **Nov 29, 2022**
Date of Publishing: **Feb 01, 2023**