Original Article

Comparative assessment of dexmedetomidine and butorphanol for attenuation of etomidate-induced myoclonus: A double-blind, randomised controlled study

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ABSTRACT

Background and Aims: Etomidate is a popular induction agent, but its use is associated with myoclonus in 50%–80% of non-premedicated patients. This study aims to compare dexmedetomidine and butorphanol for their relative efficacy in preventing etomidate-induced myoclonus. **Methods:** This randomised study was conducted after obtaining institutional ethical committee clearance and written informed consent from sixty American Society of Anesthesiologists (ASA) I or II consenting patients between 18 and 60 years of age of either sex who had been scheduled for elective surgeries under general anaesthesia. Patients were randomly allocated to dexmedetomidine 0.5 μg/kg (Group D) or butorphanol 0.015 mg/kg (Group B). Both the drugs were given as an infusion over a period of 10 min before induction of anaesthesia. The primary outcome was the incidence of myoclonic movements after etomidate, and the secondary outcomes were the severity of myoclonus, changes in the haemodynamic parameters and incidence of airway complications. Normally distributed variables were compared using Student's *t*-test, and non-normally distributed variables were compared using Mann–Whitney U test. Qualitative data were analysed using Chi-square/Fisher's exact test. A *P*-value <0.05 was considered significant. **Results:** The incidence of etomidate-induced myoclonus was significantly higher in group B compared to group D ($P = 0.035$). The median (interquartile range [IQR]) of myoclonus grade in patients of group D was 0.00 (0.00–3.00), and group B was 2.50 (0.00–3.00) ($P = 0.035$). Haemodynamics and airway-related complications were comparable between the groups. **Conclusion:** Dexmedetomidine was more effective than butorphanol in preventing etomidate-induced myoclonus.

Key words: Anaesthesia, butorphanol, dexmedetomidine, etomidate, myoclonus

INTRODUCTION

Etomidate is a favoured intravenous (IV) induction agent due to its several advantages, but it has a few undesirable side effects, such as pain on injection, postoperative nausea and vomiting, adrenal suppression, superficial thrombophlebitis and myoclonus, which overshadow its advantages.[1,2] The incidence of myoclonus after etomidate administration has been reported to be as high as 50%–80% in non-premedicated patients.[3-5] Literature review advocates the use of a variety of agents for the attenuation of myoclonus, including benzodiazepines, opioids, local anaesthetics and also a smaller dose of etomidate itself, with varied results.[5-7] Dexmedetomidine, an α2 receptor agonist, has been

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used in different doses for preventing myoclonus.[1,2,8] Similarly, butorphanol, an opioid agonist–antagonist analgesic, has also been found efficacious.[3,9] However, to the best of our knowledge, the comparative assessment of butorphanol and dexmedetomidine with their lowest possible studied doses to obliviate their limitations like hypotension and bradycardia in the context of attenuating etomidate-induced myoclonus has not been reported.

Hence, this research was planned to establish their relative efficacy in preventing the incidence and severity of etomidate-induced myoclonus with haemodynamic stability. The primary outcome was the incidence of myoclonic movements after etomidate injection while comparing dexmedetomidine to butorphanol administered before induction. The severity of myoclonus after etomidate injection, changes in heart rate (HR) and mean blood pressure (MBP) after test drug injection, after etomidate administration and after intubation, and incidence of airway complications were the secondary outcome.

METHODS

This randomised, double-blind, controlled study was conducted in a tertiary care teaching centre after obtaining written informed consent from the participants and confirming the use of patient data for research and educational purposes. The study was carried out in accordance with the principles of the Declaration of Helsinki 2013, following the ethical principles for medical research in human subjects. It was approved by the Institutional Ethics Committee (vide approval number IECHR/2020/PG/47/5 dated 21 December 2020). The trial was registered with Clinical Trials Registry-India (CTRI) (registration number CTRI/2021/01/030855, www.ctri.nic.in).

Sixty American Society of Anesthesiologists (ASA) physical status I or II consenting patients between 18 and 60 years of age of either sex who had been scheduled for elective surgical procedures under general anaesthesia were enrolled. Patients with a history of upper respiratory infection during the two weeks before surgery, allergy to dexmedetomidine or butorphanol, any analgesic or sedative administration within the previous 24 h, and pregnant women were excluded from the study.

In the operating room, after attaching standard monitors, a wide-bore IV catheter was inserted in a vein on the dorsum of the hand, and Ringer's lactate infusion was started. The baseline haemodynamic parameters (T0), including HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and MBP, were recorded. Patients were randomised into two groups of 30 each using simple randomisation by a computer-generated random number table and sequentially numbered sealed opaque envelopes prepared for allocation concealment. The test drug was prepared by an individual not involved in the study, the patient and the investigator were blinded to group allocation. Patients in group B were administered IV 0.015 mg/kg butorphanol, and in group D received 0.5 μg/kg dexmedetomidine, which were diluted in 20 ml normal saline and administered slowly over 10 min. Thereafter, anaesthesia was induced with etomidate 0.3 mg/kg IV slowly over 30 s, during which all haemodynamic variables were monitored at 1-min intervals (T1–T10). After anaesthesia induction with etomidate, the participants were watched for the occurrence of myoclonus for the next 1 min using the grading where 0 = no myoclonus, 1 = mild myoclonus (only mild fasciculation involving the face and/or distal upper and/or lower extremities), 2 = moderate myoclonus (marked movements of the face and/or limbs) and 3 = severe myoclonus (involving the limbs and trunk).[10] After 1 min of observation for myoclonus, anaesthesia induction was completed using fentanyl 2 μg/kg for adequate analgesia and IV vecuronium 0.1 mg/kg to facilitate tracheal intubation in both groups. The haemodynamic parameters were recorded after etomidate induction (T11) and endotracheal intubation (T12). Maintenance of anaesthesia was done with oxygen, nitrous oxide and sevoflurane. The end-tidal carbon dioxide concentration was kept between 35 and 40 mmHg by mechanical ventilation. Upon surgical completion, the residual neuromuscular blockade was antagonised with IV neostigmine and glycopyrrolate.

The primary outcome measure was the incidence of myoclonic movements after etomidate induction. The severity of the myoclonic movements, which was graded following etomidate induction, changes in haemodynamic variables at various time intervals, about the time from initiation of the test drug till endotracheal intubation, and the incidence of airway complications like laryngospasm and bronchospasm in both the study groups were included as secondary outcome measures.

The sample size was calculated based on a previous study by Luan *et al*.[1], who observed that the incidence

of myoclonus with 0.5 μg/kg dexmedetomidine was 36.7%. To detect an inferiority margin with a difference of 0.35 in the incidence of myoclonus between 0.5 μg/kg dexmedetomidine and 0.015 mg/kg butorphanol, the minimum required sample size with 80% power of the study and 5% level of significance was 28 patients in each study group. To reduce the margin of error, the total sample size was as 60 patients.

Data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software version 25.0 (IBM, Chicago, IL, USA). The statistical analysis was done by presentation of the categorical variables in the form of numbers and percentages. On the other hand, the quantitative data with normal distribution were presented as the mean (standard deviation [SD]) and the data with non-normal distribution as the median with 25th and 75th percentiles [interquartile range (IQR)]. Data normality was checked by using the Kolmogorov–Smirnov test. In the cases in which the data was not normal, we used non-parametric tests. Variables which were quantitative and not normally distributed in nature, that is, myoclonus grade, were analysed using Mann–Whitney test, and variables which were quantitative and normally distributed in nature, that is, age and weight, were analysed using the independent *t*-test. Repeated measure analysis of variance (ANOVA) was used to compare HR and mean arterial pressure at different periods between the groups, followed by Bonferroni correction *post hoc* comparison for significant results. Qualitative variables, such as gender and incidence of myoclonus, were analysed using the Chi-square test. Fisher's exact test was used for ASA grade and severity of grade. For statistical significance, a *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Seventy patients were assessed for eligibility, and 60 patients were randomly allocated to the two groups [Figure 1]. The demographic parameters were comparable in both groups [Table 1].

The incidence of etomidate-induced myoclonus was higher in group B (21 patients out of 30) compared to group D (13 patients out of 30) ($P = 0.035$). Nine patients in group D and 15 in group B had severe myoclonus. The median (IQR) for myoclonus grade in patients of group D was 0.00 (0.00–3.00), and in group B, patients were 2.50 (0.00–3.00) ($P = 0.035$) [Table 2].

HR of the two groups was comparable at all time points ($P = 0.608$) [Table 3]. On *post hoc* comparison, a significant difference was seen in HR within the groups at T0, T1, T2 and T3 when compared to T10 and between T9, T10, T11 and T12, with a *P*-value of 0.001 across time. MBP of the two groups was comparable at all time points, with a *P*-value of 0.268 between the groups [Table 3]. On *post hoc* comparison for the time period, a significant difference was seen in MBP within the groups at T0 and T1, between T1, T6 and T11 values and the T9 value, and between T10 and T11. No incidence of laryngospasm and bronchospasm was noted in either group.

DISCUSSION

We observed a statistically significant reduction in the incidence and median myoclonus grade severity of etomidate-induced myoclonus with dexmedetomidine compared to butorphanol.

The actual mechanism of etomidate-induced myoclonus remains an enigma to date. However, many theories have been postulated to explain this, which include a seizure-like activity, suppression of inhibitory pathways before the excitatory ones after etomidate injection and activation of spontaneous nerve transmissions.[11,12] There is a never-ending pursuit among anaesthesiologists to find an ideal drug to attenuate etomidate-induced myoclonus, which would possess attributes like having a short duration of action with minimal systemic effects and without prolonging the duration of anaesthesia. The various agents that have been employed to suppress this effect include midazolam,[6,7] fentanyl,[13] remifentanil,[14]

Table 1: Patient characteristics

Parameters	Group D (*n*=30)	Group B (*n*=30)
Age (years)	33.77 (11.64)	31.90 (12.87)
Weight (kg)	58.03 (5.65)	55.93 (6.86)
Sex (M:F)	6:24	5:25
American Society of Anesthesiologists physical status (I:II)	25:5	28:2

Values are represented as mean (standard deviation) or numbers

Table 2: Incidence and severity of etomidate-induced myoclonus between the two groups

	Group D (*n*=30)	Group B (*n*=30)	*P*
Median myoclonus grade	0.00 [0.00-3.00]	2.50 [0.00-3.00]	0.036
Severity grade			
None:mild:moderate:severe	17:4:0:9	9:2:4:15	
Incidence of myoclonus	13	21	0.035

Values are represented as Median [interquartile range] or numbers

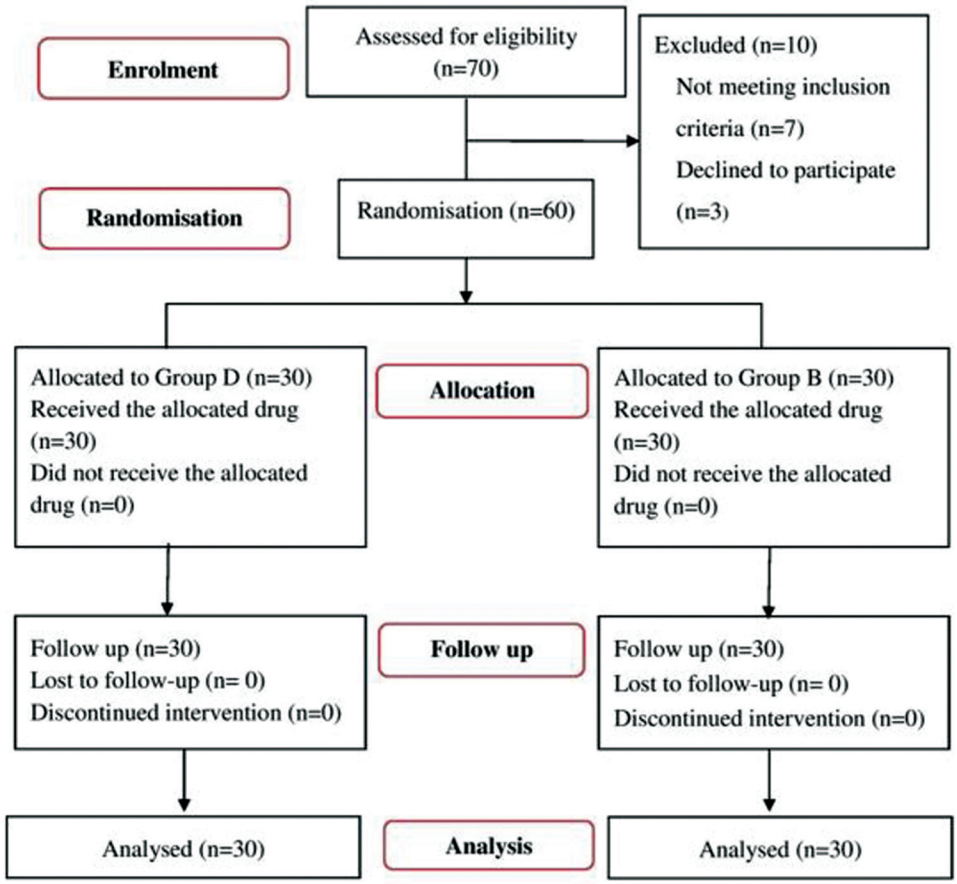

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

magnesiumsulphate,[10,15] lignocaine,[16] butorphanol,[3,9,17,18] dexmedetomidine,[1-2,8,19-22] thiopental[21] and sub-hypnotic doses of etomidate.[23] Dexmedetomidine has the edge over the other agents, given its diverse actions, including conscious sedation, analgesia and preventing haemodynamic response to laryngoscopy and intubation.

Luan *et al*.[1] concluded that the incidence of myoclonus was significantly reduced when dexmedetomidine was administered in doses of 0.5 and 1.0 μg/kg. This was compared to the control group using normal saline; no statistical significance was found in the group using the elevated dose. Also, the incidence of severe sinus bradycardia was observed to a greater extent in the 1 μg/kg dexmedetomidine group compared to a dose of 0.5 μg/kg. Gupta *et al*.[8] reported similar findings indicating no added benefit by using a higher dose of dexmedetomidine for suppressing etomidate-induced myoclonus. Therefore, we used dexmedetomidine 0.5 μg/kg to obtain an optimal attenuation and avoid possible adverse effects like hypotension and bradycardia on using dexmedetomidine 1 μg/kg.

Butorphanol has been studied in doses ranging from 0.015 mg/kg to 2 mg as a pre-treatment to reduce this myoclonus.[2,18,19] A similar dose like ours, 0.015 mg/kg, has been observed to be beneficial for reducing the incidence and severity of etomidate-induced myoclonus by Liang He *et al*.[17] without any adverse effects of hypotension and bradycardia. In the study by Pal *et al*.,[9] butorphanol was administered in two doses of 0.02 and 0.04 mg/kg, where both doses were concluded to be equally effective in attenuating the incidence and severity of etomidate-induced myoclonus, with a greater incidence of postoperative complications observed with the higher dose. Hence, considering safety with the lowest dose of 0.015 mg/kg, we used this one to prevent etomidate-induced myoclonus.

In the present study, the incidence of etomidate-induced myoclonus in the dexmedetomidine group was in concordance with the findings of studies by Luan *et al*.,[1] Gunes *et al*.,[19] Mizrak *et al*.[21] and Miao *et al*.,[22], where it was compared to other agents (midazolam, thiopentone and placebo) and in a dose of 0.5 μg/kg. This denotes that dexmedetomidine in a

Table 3: (a) Comparison of the intraoperative heart rate (beats/min)

Time	Group D (*n*=30)	Group B (*n*=30)
T0	91.00 (19.65)	87.67 (16.97)
T1	92.37 (17.74)	89.83 (15.13)
T2	91.17 (16.30)	89.03 (15.13)
T3	89.03 (15.04)	91.77 (15.41)
T4	87.67 (20.77)	96.77 (18.45)
T5	91.17 (17.68)	97.03 (16.82)
T6	90.63 (23.02)	95.83 (18.67)
T7	91.10 (19.57)	92.70 (17.11)
T8	97.40 (17.11)	97.33 (16.74)
T9	98.93 (19.59)	98.83 (15.18)
T10	92.83 (17.58)	96.73 (15.68)
T11	92.33 (17.03)	93.27 (15.61)
T12	90.10 (17.03)	88.37 (15.08)
P-value between groups	0.608	
P-value across time	0.001	

(b) Comparison of intraoperative mean blood pressure (mmHg)

Time	Group D (*n*=30)	Group B (*n*=30)
T0	83.57 (15.80)	83.17 (9.42)
T1	79.83 (14.87)	79.47 (13.12)
T2	82.50 (12.17)	80.00 (11.72)
T3	84.50 (14.22)	80.20 (12.91)
T4	88.03 (22.60)	84.30 (20.80)
T5	84.93 (20.83)	81.67 (16.26)
T6	79.90 (17.17)	78.83 (14.82)
T7	81.97 (16.94)	82.17 (17.32)
T8	84.47 (21.88)	86.73 (15.75)
T9	90.77 (16.05)	86.15 (7.76)
T10	87.60 (18.66)	84.37 (21.69)
T11	75.40 (14.99)	84.37 (21.70)
T12	87.03 (15.06)	75.63 (11.34)
P-value between groups	0.268	
P-value across time	0.016	

Values are expressed as mean (standard deviation). T0 - baseline, T1-1 min after test drug administration, T2-2 min after test drug administration, T3-3 min after test drug administration, T4-4 min after test drug administration, T5-5 min after test drug administration, T6-6 min after test drug administration, T7-7 min after test drug administration, T8-8 min after test drug administration, T9-9 min after test drug administration, T10-10 min after test drug administration, T11 - after etomidate induction, T12 - after endotracheal intubation

dose of 0.5 μg/kg showed almost uniform prevention of myoclonus across different populations.

We observed the incidence of myoclonus to be significantly higher in the butorphanol group than in the dexmedetomidine group. Our finding is in contrast to the finding of Liang He *et al*.[17], in which butorphanol was compared to normal saline used in a similar dose as ours. Similarly, a systematic review and meta-analysis conducted by Hua *et al*.[18] comprising six randomised controlled trials with butorphanol in doses of 0.015 mg/kg to 2 mg compared to a placebo, concluded that butorphanol effectively attenuated the incidence and severity of etomidate-induced myoclonus without any increase in adverse events. The anticonvulsant action of butorphanol was attributed to its interaction with multiple neurotransmitter systems, including opioid, gamma-aminobutyric acid (GABA) and *N*-methyl-d-aspartate (NMDA) receptors, and primarily the κ receptors, for which its binding ratio is favourable. One of the limitations of this meta-analysis mentioned by the authors was that different doses of butorphanol were compared with varied lengths of the observation period for myoclonus, thus leaving the window for ascertaining the optimal safe dose.

In the current study, patients from the dexmedetomidine group had a statistically significant reduction in the median myoclonus severity grade compared to the butorphanol group patients. However, this finding is in contrast to the results of Ghodki and Shetye,[2], where a significant attenuation in the median intensity of grade 2 myoclonus was observed with magnesium sulphate (30 mg/kg) compared to dexmedetomidine (0.5 μg/kg), thus indicating the potential of further exploring its effective dose in subsequent studies.

In the present study, no significant haemodynamic instability occurred, and none of the patients had any perioperative complications, that is, laryngospasm and bronchospasm, in either of the groups.

Our study had a few limitations. Firstly, the patients belonged to ASA I or II, which do not represent the ideal choice for etomidate as an induction agent. Secondly, after the etomidate, the patients were watched for myoclonic movements for 1 min; this time varies between 1 and 3 min in different studies. Thirdly, the depth of anaesthesia could not be monitored during induction, possibly contributing to a lighter plane leading to the development of myoclonus at this stage. Further research on the comparison of different doses of dexmedetomidine, above or below the one administered in the present study to attenuate etomidate-induced myoclonus, would yield clarity with regards to determining the optimal lowest dose of dexmedetomidine for prevention of etomidate-induced myoclonus.

CONCLUSION

We conclude that dexmedetomidine 0.5 μg/kg is superior to butorphanol 0.015 mg/kg in reducing both the incidence and severity of myoclonus with preserved haemodynamics.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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