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ATTENUATION OF ETOMIDATE INDUCED MYOCLONUS WITH DEXMEDETOMIDINE, MIDAZOLAM OR SALINE – A RANDOMIZED CONTROL STUDY

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ABSTRACT **Background**: An ideal premedication agents like dexmedetomidine, midazolam should be administered before induction of anaesthesia to attenuate the etomidate-induced myoclonus (EM). **Aim and Objectives**: To compare the pretreatment effect of dexmedetomidine and midazolam in attenuation of etomidate-induced myoclonus during induction of general anaesthesia. **Methods:** Ninety patients aged between 18 to 60 years of either sex belonging to ASA I and II undergoing elective surgery under GA were randomly allocated to receive intravenous study drug before induction of anaesthesia with etomidate over 60 secs, Group D– 0.5µg/kg Dexmedetomidine diluted up to 5 ml NS (n = 30), Group M – 0.05 mg/kg Midazolam diluted up to 5 ml NS (n = 30), Group C- 5 ml NS (n=30). Following completion of the study drug administration, GA is induced with etomidate 0.3mg/kg intravenously (iv) over 10 seconds. The patients were observed for myoclonus up-to 2 minutes after induction with etomidate and the study was taken as complete at this point. **Results:** The incidence of EM was significantly reduced in group D-10(33.3%) and group M-12(40.0 %), compared to group C-26(86.7%), (P< 0.0001). The severity of myoclonus was also reduced in the group D {grade1=7(23.3%), grade2=3(10%), grade3=0}and group M {grade1=7(23.3%), grade2=4(13.3%), grade3=1(3,3%)} than that in the control group {grade1=14(46.7%), grade2=8(26.7%), grade3=4(13.3%)}, (P=0.0001). **Conclusion:** Pretreatment with Dexmeditomidine or Midazolam just before induction of general anesthesia with etomidate can reduce both the incidence and severity of EM without causing any side effects. Dexmeditomidine was found to be superior to midazolam.

KEYWORDS : Dexmedetomidine, Midazolam, Etomidate Induced Myoclonus, Pretreatment.

INTRODUCTION

Etomidate, a potent hypnotic agent with rapid onset of action and clearance, stable cardiovascular profile, and minimal respiratory side effects with low histamine release, is widely used as an intravenous induction agent for hemodynamically unstable patients.[1,2,3]

Previous studies reported that the usual induction doses of etomidate does not cause significant changes in hemodynamic profile in pediatric and adult patients undergoing congenital cardiac shunt surgery.[4] However, etomidate can generate myoclonus as high as 50%-80% in non-premedicated patients during induction of anesthesia.[5,6,7,8]

Etomidate induced Myoclonus (EM) can lead to muscle fiber damage, myalgia, elevated serum potassium, risk of aspiration in patients with a full stomach, increase intraocular pressure and cause problems in patients with perforating eye injuries.[9]

The cause of EM is still not clear. Various pharmacological approaches such as opioids, benzodiazepines, lidocaine, N-methyl D-aspartate, muscle relaxants, and dexmedetomidine have been reported to attenuate the EM[10,11] myoclonus. An ideal pretreatment agent should be short acting with limited effects on stable hemodynamics and respiration.

Dexmedetomidine is a highly selective alpha2-adrenergic receptor agonist having a half-life of distribution of about 6 minutes, and an elimination half-life of 2-3 hours. The effect of dexmedetomidine in relieving myoclonus may be related to the sedative and analgesic effects.[12]

Midazolam is a short-acting benzodiazepine that causes dose dependent respiratory depression, sedation, fall in blood pressure (BP), amnesia and no analgesic property. However, the prevention of myoclonus by midazolam is not clear but may be a result of inhibition in the central nervous system.[13]

The aim of this study was to compare the effect of pretreatment with dexmedetomidine and midazolam on the incidence and severity of myoclonic movements during induction of general anesthesia with etomidate.

METHODS:

After approval from Ethics Committee at the Regional Institute of Medical Sciences, Imphal, Manipur University (A/206/REB-Comm (SP) /RIMS / 2015/526/4/2019), with CTRI No. CTRI/2021/07/035043 and obtaining written informed consent from participants, this randomized double-blinded controlled study was conducted on 90 patients of ASA I and II between 18-60 years of either sex with 40-75 kgs of body weight undergoing elective surgeries under general anaesthesia. Patients with hepatic, renal, and neurological disorders; history of allergy to study drugs, compromised cardiovascular and respiratory problems, anticipated difficult airways, patients who took analgesic drugs preoperatively and patients with morbid obesity were excluded from the study. The pre-anesthetic assessment was conducted uniformly [13] in all the patients, and premedicated only with Tab Ranitidine 300 mg orally the night before surgery and kept nil orally preoperatively.

Determination of Sample size:

Based on a previous study by Patel MH et al,[12] a sample size of 90 was calculated using a web-based sample size calculator with α value of 0.05 and power of study 0.8.

Formula: $N = \frac{(U+V)2[P1(100-P1)+P2(100-P2)]}{(P1-P2)2}$

Where,

U = 1.96 and V = 0.8452

p1 = Incidence of myoclonus while using midazolam = 40%

P2 = Incidence of myoclonus while using only saline = 86%

Hence, the calculated sample size was n = 30 in each group.

Randomization:

By computer-generated randomization, patients were divided into three groups of 30 patients each. Randomization assignment was kept in sealed opaque envelopes opened at the time of the study drug preparation. The study drugs were prepared in identical 5 ml syringes outside the operation theatre and were labeled as the "study drug" by another anesthesiologist not involved further in the study. Depending upon the drug used as premedication the patients in Group D (n=30) received iv dexmedetomidine 0.5µg/kg diluted up to 5 ml normal saline (NS), Group M (n=30) received iv midazolam 0.05 mg/kg

diluted up to 5ml of NS, Group C (n=30) received iv normal saline 5ml. The patients as well as the anesthesiologist performing the induction were blinded to the group allocation.

Procedure:
On arrival in the operation theater, an IV cannula of 18-gauge was secured on the dorsum of the hand and connected to a maintenance fluid. Electrocardiogram, pulse oximetry, and noninvasive blood pressure were connected and monitored. The study drug was injected over 60 seconds while the patient was provided with 100% oxygen via a face mask. Two minutes after administration of the study drug, induction of anaesthesia was achieved with etomidate 0.3mg/kg given intravenously over 10 seconds.

After etomidate injection, patients were observed by an observer unaware of the group allocation for 2 min for the presence of myoclonus defined as "involuntary short muscle contractions leading to short observable movements in the part of the body."[5] The intensity of myoclonus was graded clinically according to the four-point intensity scale for a period of 2 minutes: 0-No myoclonus; 1-Mild myoclonus (mild movements of a body segment e.g. a finger or a wrist); 2-Moderate myoclonus (mild movements of two different muscles e.g. face and arm); 3-Severe myoclonus (intense tonic movements in two or more muscle groups e.g. fast adduction of a limb).[5,11,14] The study was taken as complete at this point and further anesthetic technique was not influenced by this study. The anesthetic procedure was continued according to standard protocol. Butorphanol as analgesic was used in all the cases at a dose of 15µg/kg body weight 5 minutes after the induction of anaesthesia.

Statistical Analysis:
The data were entered in SPSS 21.0 for windows (Statistical Package for Social Sciences, Chicago, IL, USA). The continuous data were expressed as mean standard deviation, whereas the categorical data including the incidence and severity of myoclonus were expressed as ratios. The data were analyzed 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:
The patients in the study groups were comparable for age, weight, sex, ASA physical status, which was not statistically significant ($p > 0.05$) [Table/Fig 1].

Table/Fig 1. Demographic profiles of the 3 study groups.

Demographics	Gr D	Gr M	Gr C	P- Value
Age (yrs)	37.70 ± 10.85	37.73 ± 11.50	37.80 ± 10.94	0.955
Weight (kg)	59.18 ± 9.55	59.65 ±9.26	59.90 ± 9.45	0.956
Sex (M:F)	20:10	18"12	19:11	0.866
ASA grade (I/II)	21/9	20/10	18/12	0.709

Table/Fig 2: Comparison of incidence of myoclonus in the three groups

Myoclonus incidence	Group D	Group M	Group C	P-value
	No./Percentage	No./Percentage	No./percentage	0.000
Absent	20 (66.67%)	18 (60.0%)	4 (13.33%)	
Present	10 (33.33%)	12 (40.0%)	26 (86.67%)	
Total	30	30	30	

Myoclonus was seen in 10 patients (33.3%), 12 patients (40%) and 26 patients (86.7%) in Group D, M and C respectively (Table/Fig-2). Whereas myoclonus was absent in 20 patients (66.7%), 18 patients (60%) and 4 patients (13.33%) in Group D, M and C respectively as shown in Table/Fig 2. There was a statistically significant reduction in the incidence of myoclonus in Group D and Group M compared to Group C ($P<0.05$).

Table/Fig 3: Comparison of grades of Myoclonus in the three groups

Myoclonus intensity (grades)	Group D		Group M		Group C		P-value
	No.	(%)	No.	(%)	No.	(%)	
0(No myoclonus)	20	66.7%	18	60.0%	4	13.3%	0.001
1(Mild myoclonus)	7	23.3%	7	23.3%	14	46.7%	
2(Moderate myoclonus)	3!	10.0%	4!	13.3%	8	26.7%	
3(Severe myoclonus)	0*	0.0%	1*	3.3%	4	3.3%	
Total	30		30		30		

* > 0.05; ! > 0.05

As shown in Table/Fig 3, severity of myoclonus is lower in Dexmeditomidine and Midazolam groups compared with control (Saline) group.

DISCUSSION
The present study was conducted to evaluate the efficacy of pre-treatment with dexmedetomidine and midazolam to prevent etomidate induced myoclonus. Our study demonstrated that intravenous dexmedetomidine and midazolam pre-treatment reduced the intensity and severity of EM. Dexmedetomidine and midazolam come close to being an ideal pre-treatment for the attenuation of EM in that it has a rapid onset and short duration of action with minimal cardio-respiratory depression and does not prolong recovery from anaesthesia in the clinically used dose.[13]

In the present study, we found a statistically significant decrease in the incidence of EM in patients pre-treated with 0.5 µg/kg Dexmedetomidine (33.3%) and 0.05 mg/kg Midazolam (40%) compared with placebo group (86.7%) ($P<0.05$). Patel MH et al [12] reported a statistically significant decrease in the incidence of etomidate-induced myoclonus in patients pre-treated with 1µg/kg Dexmedetomidine (33.3%) and 0.05 mg/kg Midazolam (40%) compared with placebo group (86.7%) ($P=0.002$). Aktolga et al [15] also reported that pre-treatment with Dexmedetomidine (1 µg/kg) and Midazolam (0.05 mg/kg) is effective in reducing the incidence of etomidate-induced myoclonic muscle movements. The incidence of myoclonus was significantly low in Dexmedetomidine and Midazolam groups (30%, 37%) than in the control group (90%) ($P<0.05$). Our study findings are comparable with the above two studies which we could achieve with a lower dose of dexmedetomidine.

Luan HF et al [16] concluded that pre-treatment with dexmedetomidine at two different doses of 0.5 and 1 µg/kg significantly reduced the incidence of EM (30.0 and 36.7%) compared to placebo (63.3%). However, they found that there is no significant difference between the two doses, but recommended 0.5 µg/kg dexmedetomidine as it has lesser incidence of side effects like bradycardia and hypotension. Mizrak et al [17] reported an incidence of myoclonus with Dexmedetomidine pre-treatment as 34%. These findings were consistent with our study.

Dey S and Kumar M [13] reported a significant decrease in the incidence of myoclonus from 87.5% (Midazolam) to 45% (Dexmedetomidine) thereby, proving the efficacy of Dexmedetomidine suppressing EM as compared to midazolam. Isitemiz et al [4] found the incidence of myoclonus to be 70% following premedication with 0.03 mg/kg midazolam. In our study also, we found a lesser incidence of myoclonus with dexmedetomidine than midazolam. However, the incidence of myoclonus in the midazolam group of these two studies were very high, in contrast to our study and some other previous studies of the same genre. This starking difference is due to the low doses of midazolam used by them (0.015 and 0.03 mg/kg) as compared to the dose of 0.05 mg/kg in our study and the comparable doses of the other studies

Dexmedetomidine is a highly selective alpha2-adrenergic receptor agonist commonly found in synapses, post synaptic part of the central nervous system, peripheral nerves and autonomic ganglia. Stimulating synaptic alpha 2-receptors in sympathetic nerve endings can inhibit the release of norepinephrine. Before anaesthesia, intravenous injection of the drug can significantly reduce the stress responses to laryngoscopy and endotracheal intubation, and can reduce the dose of propofol and opioids. Therefore, the effect of dexmedetomidine in relieving myoclonus may be related to the sedative and analgesic effects.[13,16]

Midazolam is a short-acting benzodiazepine that causes dose dependent respiratory depression, sedation, fall in blood pressure (BP), amnesia and no analgesic property. The inhibitory effects of midazolam on central nervous system act through Gamma-aminobutyric acid ($GABA_A$) receptors. The site of action where

midazolam prevent the myoclonus occurring after etomidate injection is not clear. However, the prevention of myoclonus by midazolam is a result of inhibition in the central nervous system.[18,19]

The involuntary myoclonic movements seen with etomidate are believed to be caused by subcortical disinhibition.[6] A large dose of etomidate depresses the cortical activity before depressing subcortical activity, thereby causing myoclonus.[20] The potential mechanism of myoclonus resulting from etomidate use is still unclear. Many reports have linked such involuntary movements either to a seizure like activity or disinhibition phenomenon with earlier suppression of the cortical before subcortical activity.[21,22] Disruption of the cortical GABA- mediated inhibition makes skeletal muscles susceptible to the spontaneous nerve transmissions, thereby leading to the myoclonic movements.[4] The mechanism behind the etomidate induced myoclonus has also been postulated to be similar to convulsive seizures.[4,21,22] The incidence of myoclonus has been shown to increase with the speed of etomidate administration and the period of observation.[23] And that inhibitory circuits can be depressed earlier and at lower concentrations than excitatory neuronal circuits. We hypothesized that the excitatory phenomenon of myoclonus was caused by disequilibrium of the drugs at the various effect sites in the central nervous system (CNS). Differences in local cerebral blood flow or affinity might produce a temporary disequilibrium of effect, resulting in more rapid inhibition of cortical depression. If over time, inhibitory and excitatory neuronal circuits are both depressed by etomidate, but the inhibitory are depressed sooner, then pre-treatment could reduce the incidence of myoclonus. Conversely, larger initial bolus doses (up to a point), increase the incidence of myoclonus.

In our study Dexmedetomidine and Midazolam was administered 2 minutes before etomidate (0.3mg/kg) injection. 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 in approximately 50% of the episodes occur after the first minutes as reported by Sidighinejad A et al.[19] In majority of the patients in among the three groups of the present study, myoclonus occurred within two minutes after the start of induction as also reported by Mullick P et al.[24] The period of observation for myoclonus varied from one to three minutes in most of the previous studies suggesting that the actual incidence of etomidate induced myoclonus may be higher than that the 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.

Limitation

The main limitation of our study was that we evaluated only one dose each of dexmedetomidine and midazolam, chosen based on previous studies.[12] Further studies are required to determine the minimum doses that will suppress myoclonic movements without causing any adverse effects. Also, our study didn't evaluate the duration of myoclonus, which is as relevant as the incidence and hence further studies are warranted in this regard. It's use in patients with comorbid conditions and high-risk cases needs further evaluation.

CONCLUSION

In this study, we found that there was statistically significant reduction in the incidence of myoclonus among the dexmedetomidine and midazolam groups (Group D and Group M), as compared to the normal saline group (Group C) (P value <0.05). Dexmedetomidine was found to be comparatively better than midazolam but statistically insignificant, and may be recommended as a premedication to reduce the incidence of EM. Further studies are required to determine their minimum doses that will suppress myoclonic movements without causing any adverse effects. However, a cost-benefit analysis needs to be carried out.

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