Comparison of pretreatment with dexmedetomidine with midazolam for prevention of etomidate-induced myoclonus and attenuation of stress response at intubation: A randomized controlled study

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Abstract

**Background and Aims:** Myoclonus is a common problem during induction of anesthesia with etomidate. A variety of drugs have been used to decrease the incidence of myoclonus. In this study we compared the effects of dexmedetomidine and midazolam pretreatment on the incidence of etomidate induced myoclonus. We also studied the effects of these drugs on attenuation of stress response at laryngoscopy and intubation on induction with etomidate.

**Material and Methods:** Eighty adult patients (18 to 60 years age) of either sex, American Society of Anesthesiologists physical status I and II undergoing elective general surgeries under general anesthesia were randomly allocated into two groups. Group D patients received Inj. Dexmedetomidine (0.5 µg/Kg) and Group M received Inj. Midazolam (0.015 mg/Kg) in 10 ml saline over ten minutes. Myoclonus was graded after intravenous administration of etomidate (0.3mg/Kg) and hemodynamic response to laryngoscopy and intubation were observed at various time intervals. Analysis of statistical data was done using Statistical Package for Social Sciences (SPSS) version 21.0. Quantitative variables were compared using Independent T Test/Mann Whitney test (for non-parametric data). Qualitative variables were compared using Chi-Square test/Fisher’s Exact Test. A P value of < 0.05 was considered statistically significant.

**Results:** In Group D, 22 out of 40 (55%) patients did not have any myoclonus during induction with etomidate, and none of the patients had grade 3 (severe) myoclonus. In Group M, 19 out of 40 patients (47.5%) had grade 2 (moderate) and 6 patients (15%) had grade 3 myoclonus. Stress response due to intubation was more effectively suppressed by dexmedetomidine as compared to midazolam.

**Conclusion:** Incidence of myoclonus among patients who underwent pre-treatment with dexmedetomidine was significantly lesser than those who underwent pre-treatment with midazolam. Greater degree of attenuation of stress response in the dexmedetomidine group was observed as compared to midazolam group.

**Keywords:** Dexmedetomidine, etomidate, midazolam, myoclonus

Introduction

Etomidate is an imidazole-derived sedative-hypnotic agent directly acting on gamma-aminobutyric acid (GABA) receptor complex, blocking neuroexcitation, and producing anesthesia. It has a stable hemodynamic profile and minimal effects on the respiratory system as compared to other induction agents. Pain on injection and myoclonus is the most common side effects of this drug. It has been abolished by the new fat emulsion preparation of etomidate,
but the new solvent has not reduced the incidence of myoclonus.\textsuperscript{[2]}

Myoclonus is a common problem during the induction of anesthesia with etomidate; up to 80% of the nonpremedicated patients develop myoclonic movements, which may be a problem in nonfasting patients because of the risk of hypoventilation as well as regurgitation and aspiration.\textsuperscript{[3-5]}

The present study has been designed to ascertain an ideal pretreatment drug which can abolish or significantly reduce the incidence of etomidate-induced myoclonus and also cause attenuation of stress response of laryngoscopy and intubation. The primary aim of our study was to compare the incidence and severity of myoclonus in both the study groups. The secondary objective was to compare the attenuation of hemodynamic changes of laryngoscopy and intubation in both the groups.

**Material and Methods**

This prospective, randomized, double-blind comparative study was conducted at a tertiary care hospital from January 1, 2014, to April 30, 2015. After approval from the Institutional Review Board, 80 adult patients between 18 and 60 years, scheduled for elective surgery under general anesthesia were recruited for the study. Patients of either sex with the American Society of Anesthesiologists (ASA) physical status Grade 1 or 2, who were willing to give consent were included in the study. Patients with a history suggestive of allergy to any of the study medications, anticipated difficult airway, known psychiatric disorders, sepsis or systemic infections and with pacemakers or on beta blockers or having heart blocks were excluded from the study. The patients were randomly allocated into one of the two study groups. Group D received injection dexmedetomidine infusion (0.5 µg/kg) in 10 ml saline over 10 min before the induction of anesthesia. Group M received injection midazolam (0.015 mg/kg) in 10 ml normal saline over 10 min before the induction of anesthesia. Syringes containing aqueous solution of either drug were prepared in a double-blind fashion by a team member who was not involved in the data recording. All patients were subjected to a detailed preanesthetic evaluation. Premedication was done with tablet alprazolam 0.25 mg the night prior and 2 h before surgery. Inside the operation theater, standard monitors were applied. After intravenous cannulation, the following baseline parameters were noted: heart rate (HR), blood pressure (BP) (systolic, diastolic, mean), pulse oximetry (SpO\textsubscript{2}), and electrocardiogram. Patients in Group D and Group M received injection dexmedetomidine infusion (0.5 µg/kg) and injection midazolam (0.015 mg/kg), respectively in 10 ml normal saline over 10 min followed by injection etomidate (0.3 mg/kg) over 30 s or till the abolition of eyelash reflex was observed. Injection fentanyl (2 µg/kg) was then administered followed by Injection vecuronium (0.1 mg/kg body weight) to facilitate intubation. Positive pressure ventilation was initiated using bag and mask for 3 min with N\textsubscript{2}O:O\textsubscript{2}(70:30) and isoflurane (0.4%–0.8%) as an inhalational agent. Orotracheal tube intubation was done with an appropriate sized cuffed endotracheal tube by an experienced anesthesiologist.

After the injection of study drug and etomidate, the presence of myoclonus was recorded in all patients and if present, the severity was graded by a person blinded to the treatment group. Myoclonus was defined as involuntary, short contraction of some muscle fibers, of a whole muscle, or of different muscles of one group leading to short observable movements of the corresponding body parts. The intensity of myoclonus was graded as follows:

- 0 - no myoclonus
- 1 - mild myoclonus (short contraction of some muscle fibers e.g., a finger or shoulder)
- 2 - moderate myoclonus (contraction of different groups of muscles, e.g., face and leg)
- 3 - severe myoclonus (intense clonic movement in two or more muscle groups, e.g., fast adduction of a limb or whole body movements).\textsuperscript{[3]} All the hemodynamic parameters were recorded at the following intervals:

- TB - baseline (before the start of dexmedetomidine/midazolam)
- TA - after study drug infusion
- T0-3 min after induction and before intubation
- T1-1 min after intubation
- T3-3 min after intubation
- and T5-5 min after intubation.

**Statistical analysis**

On the basis of pilot study, the incidence of etomidate-induced myoclonus in dexmedetomidine group was 50% and in Midazolam group was 83.3%. Taking these values as reference, the minimum required sample size with 90% power of the study, and a Type I error of 0.05 is a total of 37 in each group. Hence, total sample size taken was 80 (40 per group). Quantitative variables were compared by independent t-test/Mann–Whitney test (for nonparametric data). Qualitative variables were compared using Chi-square test/Fisher’s exact test. \( P < 0.05 \) was considered to be statistically significant. The analysis was done using Statistical Package for Social Sciences version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).
Results

In our study, there was no significant differences among the two groups regarding age, weight, sex and ASA physical status. It was seen that patients who received pretreatment with dexmedetomidine had lower incidence of myoclonus after induction with etomidate than those who received pretreatment with midazolam [Figure 1]. In our study, 55% of patients who were pretreated with dexmedetomidine before induction with etomidate had Grade 0 myoclonus as compared to 12.5% in the midazolam group, thereby proving the efficacy of dexmedetomidine suppressing etomidate-induced myoclonus as compared to midazolam. 35% of the patients in the dexmedetomidine group had Grade 1 myoclonus as compared to 25% of patients in the midazolam group. 10% of patients in the dexmedetomidine group had Grade 2 myoclonus as compared to 47.5% in the midazolam group. 7.5% of patients in midazolam group experienced Grade 3 myoclonus whereas none of the patients in the dexmedetomidine grouped Grade 3 myoclonus. Also, pre-treatment with dexmedetomidine led to greater degree of attenuation of stress response upon laryngoscopy and intubation as compared to pre-treatment with midazolam [Figures 2 and 3].

Discussion

In this randomized, double-blind prospective clinical study, we compared the effects of dexmedetomidine and midazolam pretreatment on the incidence of etomidate-induced myoclonus and attenuation of stress response at intubation. To the best of our knowledge, there is paucity of literature studying dexmedetomidine pretreatment for etomidate-induced myoclonus. A variety of opioids such as sufentanil and remifentanil has been used to decrease the incidence of myoclonus.[6,7]

Etomidate is widely used as an anesthetic induction agent in clinical practice. Several desirable properties, such as rapid onset, brevity of action, lack of cardiovascular depression, and protection of intracranial pressure, make it an attractive agent for rapid sequence intubation. However, etomidate is also associated with side effects. It may cause temporary inhibition of steroid synthesis after single doses and infusions.[8,9] This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and high incidence of nausea and vomiting) led to several editorials questioning the role of etomidate in modern anesthesia practice.[10,11] Pain on injection has been largely eliminated by the use of a lipid formulation of etomidate, but myoclonus remains a common problem during anesthesia induction. Many mechanisms have been proposed to explain myoclonus.
For example, it was reported that myoclonus resulted from temporal subcortical disinhibition similar to irritable leg syndrome, which is characterized by uncomfortable legs, irritability, inability to sleep, and numbness, but not related to epileptic activity.\[^{3,12,13}\]

Etomidate and other hypnotics act at the GABA\(^{\text{A}}\) receptor. Low concentrations of etomidate potentiate the effect of GABA at its receptor (modulating effect); higher concentrations directly activate the receptor (activating effect). The effect of etomidate to modulate and activate GABA\(^{\text{A}}\) receptors is uniquely dependent on the beta subunit within the receptor.\[^{14-17}\]

The distinct distribution of the GABA\(^{\text{A}}\) receptor subunits within the central nervous system may explain the specific regionally distinct effects of etomidate.

Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist. Its mechanism of action is at the locus ceruleus which shows one of the highest densities of alpha-2A adrenoreceptors in the brain.\[^{18}\]

Presynaptic activation of the alpha-2A adrenoreceptors in the locus ceruleus inhibits the release of norepinephrine resulting in sedative and hypnotic effects.\[^{19}\]

Other pharmacological properties include anxiolysis, analgesia, and sympatholysis with anesthetic sparing effects and absence of significant respiratory depression. An intravenous injection of the drug can significantly reduce the stress responses of laryngoscopy and endotracheal intubation and can reduce the dose of propofol and opioids.\[^{20}\]

Therefore, the effect of dexmedetomidine in relieving myoclonus may be related to its sedative and analgesic effects.

Intravenous dexmedetomidine has also been used as a premedication in different doses, ranging from 0.2 to 2.5 \(\mu\)g/kg body weight. Menda et al. used dexmedetomidine in a dose of 1 \(\mu\)g/kg over 15 min before induction, and found that the HR was significantly lower at all times as compared to the baseline values in the intraoperative period.\[^{21}\]

Midazolam is a benzodiazepine having amnestic and sedative properties used for preoperative medication for anxiolysis and sedation, treatment of grand mal seizures. Mizrak et al. concluded that pretreatment with dexmedetomidine or thiopental is effective in reducing the incidence and severity of etomidate-induced myoclonic muscle movements. The incidence of myoclonus was significantly low in dexmedetomidine and thiopental groups (34%, 36%) than in control groups (64%) \(^{\text{P}} < 0.05\).\[^{22}\]

Isitemiz et al. used fentanyl, midazolam, and a combination of fentanyl and midazolam to prevent etomidate-induced myoclonus. They concluded that both the combination of 0.5 \(\mu\)g/kg fentanyl with 0.015 mg/kg midazolam and 1 \(\mu\)g/kg fentanyl alone were effective in the prevention of myocloni caused by anesthesia induction with etomidate and observed in high rates in patients without premedication. Premedication with 0.03 mg/kg midazolam alone was insufficient for the prevention of myoclonus.\[^{23}\]

Gunes et al. compared midazolam and dexmedetomidine for the prevention of myoclonic movements and injection pain following etomidate injection and concluded that pretreatment with both midazolam and dexmedetomidine reduced etomidate-induced myoclonus and injection pain during anesthesia induction.\[^{24}\]

Luan et al. in their study concluded that pretreatment with 0.5 and 1.0 \(\mu\)g/kg dexmedetomidine significantly reduced the incidence of etomidate-induced myoclonus during anesthetic induction; however, 0.5 \(\mu\)g/kg is the recommended dose because it has lesser side effects.\[^{25}\]

Therefore, the results of our study are in concordance with the other studies which finds dexmedetomidine efficacious in suppressing etomidate-induced myoclonus. In our study, however, midazolam did not suppress myoclonus induced by etomidate as effectively as dexmedetomidine.

The secondary objective of our study was to compare the attenuation of hemodynamic response of laryngoscopy and intubation among two groups of patients who were pretreated with dexmedetomidine and midazolam during induction with etomidate. The attenuation of the stress response during laryngoscopy in the study was greater in the dexmedetomidine group as compared to the midazolam group.

Sulaiman et al. in studied the effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. They concluded that dexmedetomidine provides good control of hemodynamics during laryngoscopy and endotracheal intubation. Dexmedetomidine at a dose of 0.5 \(\mu\)g/kg as 10 min infusion was administered before the induction of general anesthesia attenuated the sympathetic response to laryngoscopy and intubation in patients undergoing myocardial revascularization.\[^{26}\]

The main limitation of our study was that we evaluated only one dose of dexmedetomidine and midazolam based on previous studies. Further studies are required to determine the minimum doses of dexmedetomidine and midazolam that will suppress myoclonic movements without causing any adverse effects.

**Conclusion**

We conclude that the incidence of etomidate-induced myoclonus was significantly decreased among patients who...
underwent pretreatment with dexmedetomidine in comparison with midazolam. In addition there was greater degree of attenuation of stress response in the dexmedetomidine group as compared to the midazolam group.

However, a cost-benefit analysis needs to be carried out. In addition, its use in patients with comorbid conditions and high-risk cases need further evaluation.

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**Conflicts of interest**

There are no conflicts of interest.

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