To Evaluate the effect of Dexmedetomidine Pretreatment on Myoclonus during Anaesthetic Induction with Etomidate

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Abstract
Etomidate is frequently used nowadays as an inducing agent in patients with compromised cardiovascular function, but it leads to undesirable side effects like myoclonus during induction. Several drugs have been considered before induction to reduce the incidence of myoclonus. This prospective, randomized double blinded study was aimed to compare the effect of dexmedetomidine (DEX) pretreatment on the incidence and severity of etomidate-induced myoclonus. 100 patients undergoing elective surgical procedures were randomly allocated to two groups for i.v. administration of 1.0 µg/kg DEX in 100 mL isotonic saline (group D) and 100 mL isotonic saline (group NS) 10 minutes prior to induction. All groups subsequently received 0.3 mg/kg etomidate by intravenous injection. The incidence and severity of myoclonus were recorded for 1 min after etomidate administration and the incidence of cardiovascular adverse effects were also recorded. The incidence of myoclonus was 38% was in group D and 70% in group NS. The severity of myoclonus was graded as mild, moderate and severe. In group D and group NS number of patients who had mild, moderate and severe myoclonus were 10,5,4 and 11,15,9 respectively. It was concluded that pretreatment with 1.0 µg/kg DEX significantly reduced the incidence and severity of etomidate-induced myoclonus during anaesthetic induction.

Keywords: Dexmedetomidine; Etomidate; Myoclonus.

Introduction
An ideal inducing agent for general anaesthesia should have smooth induction, good haemodynamic stability, minimal respiratory and other side effects and rapid clearance. Etomidate, an imidazole derivative has unique properties like hemodynamic stability, favorable toxicity profile and pharmacokinetics enabling rapid recovery after a single dose. Etomidate is also preferred in patients with respiratory and airway disease, intracranial hypertension and in patients with shock. However, it has two well known and disturbing side effects, injection pain and myoclonus apart from nausea and vomiting. Injection pain has been minimized by a new lipid formulation of Etomidate. However, suppression of myoclonus continues to be a clinical problem as a common
side effect of Etomidate administration during induction of anesthesia. The incidence of myoclonus has been reported to be as high as 50-80%.[4] The consequences of this side effect can be serious in non-fasted emergency patients, patients with open eye injuries, or patients with limited cardiovascular reserves.[5] In addition, during the jerky movements ECG leads can become detached. It should be noted that ECG leads detachment during myoclonic movements leads to delay of monitoring and success of early intervention.[6]

The neurologic mechanism of myoclonic activity after etomidate administration is not clear. Some studies suggested that it may be a kind of seizure activity.[6] A study that investigated EEG alterations in patients with etomidate induced myoclonus stressed the correlation between myoclonus and the increase in delta waves on EEG recordings, and it was not a typical seizure. Other studies suggested that myoclonus after etomidate administration is a result of subcortical disinhibition like that of restless leg during sleep and does not happen from epileptic focus. An unsynchronized onset of etomidate induces fasting depression of the cortex, resulting in temporary disinhibition of the subcortex resulting in inducing the myoclonic movement.[7,8]

A number of drugs have been investigated to reduce the rate and intensity of this adverse effect. Various drugs are premedicated to reduce myoclonic jerks induced by etomidate like midazolam,[9] opioids,[10] magnesium sulphate,[11] rocuronium.[12] Dexmedetomidine is among the new agents tried as premedicants to reduce myoclonus. Dexmedetomidine, an α2-adrenoceptor agonist having analgesic and anxiolytic activity, is widely used for anesthesia and intensive care.[13] Though mechanism is still not very clear, it has been recently tried to reduce the incidence and severity of myoclonus due to its anxiolytic properties and by subcortical inhibition.

This study was primarily aimed to see the efficacy of dexmedetomidine in reducing the incidence and severity of myoclonus prior to etomidate induction.

**Materials and Methods**

This randomized, double blind, prospective study was performed on 100 cases in the department of anesthesiology, Sardar Patel Medical College and Associated Group of Hospitals Bikaner after obtaining the ethical committee clearance. Hundred adult patients of either sex between age group 18 to 60 years belonging to ASA grade 1 or ASA grade 2 were included in study. They were randomized into 2 groups of 50 patients each and an effort was made that the group do not significantly differ with respect to age, weight and height.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drugs &amp; Doses</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group D</td>
<td>1μg/kg dexmedetomidine pretreatment with etomidate induction at 0.3 mg/kg</td>
<td>50</td>
</tr>
<tr>
<td>Group NS</td>
<td>100 ml saline pretreatment with etomidate induction at 0.3 mg/kg</td>
<td>50</td>
</tr>
</tbody>
</table>

After complete pre-anaesthetic assessment, the procedure was explained to the patients and written informed consent was taken one day before surgery.

Patient with known allergy to the drugs used in the study, with significant cardiac, respiratory, hepatic or renal dysfunction, an anticipated difficult airway, hypotension, history of seizure disorder, presence of primary and secondary steroid deficiency or on steroid medication were excluded from study.

The patients were shifted to the operating room with all aseptic precautions. Patients were kept NPO 8 hours prior to surgery. An intravenous line was secured. Then standard monitoring and recording of non invasive B.P., pulse rate, oxygen saturation, ECG and respiratory rate before induction of anaesthesia.

Premedication with Inj. Glycopyrrolate 0.2 mg was done. Ringer lactate was infused at a rate of 4-6 ml/min. Before anaesthesia induction in group D, 1.0 μg/kg dexmedetomidine in 100 mL isotonic saline was infused over 10 minutes. In group NS, 100 ml isotonic saline was infused over 10 minutes. When the infusion was completed 0.3 mg/kg etomidate was injected intravenously over
a period of 1 min. Patients were observed continuously for myoclonus for 1 min by a physician who was blinded to all group treatments. Myoclonic movements were defined as involuntary short muscle contractions leading to short observable movements in parts of the body. The intensity of myoclonus was graded as 0, no myoclonus; 1, mild myoclonus (short movements of a body segment, e.g., a finger or a wrist only) 2, moderate myoclonus (mild movements of two different muscles, e.g., face and leg); and 3, severe myoclonus (intense clonic movements in two or more muscle groups, e.g., fast adduction of a limb).

After administration of etomidate and evaluation of myoclonus, all patients were injected with 2 µg/kg fentanyl. One minute after the end of etomidate injection, muscle relaxation was achieved with 0.08 mg/kg vecuronium and endotracheal intubation was performed after another 2 minutes. Following etomidate injection, mask ventilation with 100% O₂ was carried out until intubation. In both the groups myoclonus, haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation) were recorded before and after premedication, before and after induction and intubation.

Maintenance anesthesia was provided by sevoflurane with 50% oxygen and nitrous oxide (N₂O) in 1:1 ratio, and Vecuronium 0.02 mg/kg as per need with controlled ventilation. Intraoperative hemodynamics parameter (heart rate, systolic blood pressure, diastolic blood pressure) were recorded every 10 minute for first hour of surgery then every 15 min till the end of surgery.

Complications like nausea, vomiting, hypotension, bradycardia, respiratory depression, agitation and arrhythmia were observed. Patient were observed for 2 hours in PACU (post anaesthesia care unit) for any postoperative complications like nausea, vomiting, hypotension, bradycardia, respiratory depression, agitation, arrhythmia. Any complication that occurs, was treated with appropriate measures.

All the data was filled up in the proforma attached and statistical analysis were performed using SPSS software to draw conclusions. Students t-test and chi-square test was used in drawing conclusions and statistical significance.

### Results

#### Demographic characteristics

<table>
<thead>
<tr>
<th>DEMOGRAPHICS</th>
<th>GROUP D</th>
<th>GROUP NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>43.72±13.12</td>
<td>43.12±13.4</td>
</tr>
<tr>
<td>SEX(M/F)</td>
<td>13/37</td>
<td>08/42</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>63.32±6.56</td>
<td>61.42±5.80</td>
</tr>
</tbody>
</table>

Data as reported as mean ±SD or number for n = 50 patients/group. There were statistically insignificant. (p value >0.05)

There were no significant differences among the 3 groups with regard to age, gender, weight, or ASA class.

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### Table showing incidence and severity of myoclonus

<table>
<thead>
<tr>
<th>MYOCLONUS</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>Number of Patients</td>
<td>Number of Patients</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Group D</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Group NS</td>
<td>11</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>

Table showing incidence and severity of myoclonus

<table>
<thead>
<tr>
<th>Myoclonus</th>
<th>Group D</th>
<th>Group NS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>0.7±1.00</td>
<td>1.36±1.09</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The total percentage of myoclonus in NS group was 70% whereas it was 38% in group D. The results remained statistically significant. (p value = 0.001)

Comparison between complications in dexmedetomidine and normal saline group

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Low blood pressure</th>
<th>Sinus bradycardia</th>
<th>PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP D</td>
<td>4 (8%)</td>
<td>6 (12%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>GROUP NS</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>12 (24%)</td>
</tr>
</tbody>
</table>

Data reported as number or number and percentage =50 patients in each group.
P value >.05 in each in each group for each category
This suggested that there was no significant difference in the complications among the groups.

Discussion
Etomidate fulfills the requirement as an induction agent with stable cardiovascular and respiratory profile. But it comes with the side effects like myoclonus on induction. The consequences of this side effect can be serious.
In agreement with previous literature the use of Etomidate was found to be associated with higher incidence of myoclonus activity and upto 70 to 80% in non premedicated patients.
Myoclonus was observed in 35 patients out of 50 (70%) in NS group. Out of them 11 (22%) had mild, 15(30%) moderate and 9 (18%) had severe myoclonus. Whereas in group D where 1μg/kg dexmedetomidine was given as premedication before induction with Etomidate, the incidence of myoclonus was 38%. 10 patients (20%) had mild myoclonus, 5(10%) had moderate and 4(8%) had severe myoclonus.
The results demonstrate that premedication with1μg/kg Dexmedetomidine reduces the incidence and intensity of myoclonus.

The results of our study correlates with study of Mizrak A et al (2010) They concluded that premedication with Dexmedetomidine (0.5μg/kg) and thiopentone (1 mg/kg) are effective in reducing the incidence and severity of myoclonus induced by Etomidate.
Nevriye Salman et al (2013) concluded that Dexmedetomidine (0.5 µg/kg) and midazolam (0.25 mg/kg) both are effective in reducing the myoclonus induced by etomidate induction but midazolam had respiratory depression.
H.F.Laun et al (2014) documented that pretreatment with 0.5 and 1.0 µg/kg Dexmedetomidine significantly reduced the incidence of etomidate induced myoclonus during anesthetic induction but Dexmedetomidine with 1.0 µg/kg was associated with more side effects like bradycardia.

Limitations
Our study design had some limitation. The first is that we did not measure plasma cortisol and
adrenocorticotropic hormone levels. It has been well known that adrenocortical suppression is one of the most important adverse effects of Etomidate. Although Etomidate causes adrenocortical suppression, a single injection to induce anaesthesia will only produce a transient and clinically insignificant interference with adrenocortical function. Other limitation is that the study was conducted on a single center with small group of patients with normal LV function which will truly not reflect for very old age patient with relatively unstable haemodynamic.

Conclusion
According to our study, patients given pretreatment with 1 µg/kg Dexmedetomidine 10 minutes prior to induction with Etomidate could significantly reduce the incidence and severity of myoclonus without significant complications as compared to group NS in which pretreatment was done with Normal Saline as control group. So these characteristics indicate that Dexmedetomidine can be safely used as premedication prior to Etomidate for reduction in Etomidate induced myoclonus.

Bibliography
infusion for analgesia up to 48 hours after lung surgery performed by lateral thoracotomy. Proc (Bayl Univ Med Cent) 2014; 27: 3-10.


