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Midazolam Pre-Treatment before Etomidate Anaesthesia

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Abstract

Introduction: Etomidate a GABA receptor stimulating hypnotic agent is short-acting, has minimal residual sedation and a favourable haemodynamic profile and is thus a common choice for short term procedures especially in the haemodynamically compromised patients. But it has undesirable side effects of pain on injection and myoclonus. The problem of pain on injection has been solved by a new lipid formulation for etomidate. Myoclonus is seen in up to 50 to 80% of patients during induction of anaesthesia with etomidate if no supplemental agents are used. A number of drugs have been investigated for the suppression of etomidate-induced myoclonus. Ideally a pre-treatment drug for preventing myoclonic movements should be short acting, not have significant effects on respiration and haemodynamics and not prolong recovery from anaesthesia. Etomidate has a less inhibitory effect on the pharyngo-laryngeal reflex, hence blunting the responses to laryngoscopy and endotracheal intubation is also necessary. *Materials and Methods:* This study was conducted to study the effect of pre-treatment with midazolam on etomidate induced myoclonus.We studied 30 patients who were given Midazolam pre-treatment before administration of Etomidate. *Results:* 23.33% (7/30) patients developed myoclonus and none of them had severe myoclonus. Vital were not significantly affected. *Conclusion:* Midazolam is a good pre-treatment option before etomidate as it reduces incidence and severity of etomidate induced myoclonus without significant adverse effects.

Keywords: Cardio-stable, Etomidate, Midazolam, Myoclonus, Pain, Pre-treatment.

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Introduction

There are many anaesthetic agents for induction of anaesthesia like sodium thiopentone, propofol, ketamine, methohexital. The present financial pressure to reduce anaesthesia turnover time has created a demand for an induction agent with a rapid onset and minimal residual sedation thereby minimising the timerequired for emergence and time spent in the recovery room.

Etomidate a short acting GABA receptor stimulating hypnotic agent has manypositive characteristics like rapid onset/offset, minimal residual sedation and favourable haemodynamic profile, that is why it is common choice for short term procedures especially in the haemodynamically compromised patients [1]. It has been a preferred agent for cardiac surgeries [2,3]. Two undesirable

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side effects of etomidate are pain on injection and myoclonus. Although the problem of pain on injection has been solved by a new lipid formulation for etomidate, the problem of etomidate - induced myoclonus, especially for short term procedures has yet to be solved. Myoclonus is seen inup to 50 to 80% of patients during induction of anaesthesia with etomidate if nosupplemental agents are used [4].

Myoclonus is defined as an involuntary, short contraction of some musclefibres, of a whole muscle, or of different muscles of one group, leading to ashort observable movement of the corresponding body part usually not longerthan 100 ms [5].

The mechanism of etomidate-induced myoclonus appears to be disinhibition subcortical structures that normally suppress extra pyramidal motor activity. The fact that etomidate induced myoclonic activity may be associated with seizure activity on the EEG suggests caution in the use of this drug for the induction of anaesthesia in patients with a history of seizures.

A number of drugs have been investigated for the suppression of etomidate-induced myoclonus like benzodiazepines in the form of midazolam, flunitrazepam, diazepam, opioids in the form of fentanyl, sufentanil, remifentanil, magnesium sulfate, rocuronium, lignocaine, dexmedetomidine, rocuronium, thiopental, droperidol [6–8]. The effects of benzodiazepines on the different GABA receptors may explain the mechanism by which these drugs reduce the incidence of myoclonic movements. Ideally a pre-treatment drug for preventing myoclonic movements should beshort acting, not have significant effects on respiration and haemodynamics and not prolong recovery from anaesthesia. Moreover, etomidate being cardio-stablehas a less inhibitory effect on the pharyngo laryngeal reflex, hence blunting the responses to laryngoscopy and endotracheal intubation is also necessary especially in cardiac patients. One should keep in mind all these problems while selecting a pre-treatment drug to make etomidate an ideal induction agent. Thus. this study was conducted to study the effect of pre-treatment with midazolam on etomidate induced myoclonus.

The objective of the study was to study the effect of midazolam pre-treatment on induction with etomidate. The parameters studied were haemodynamic response to laryngoscopy and intubation during anaesthetic induction with etomidate, incidence and severity of etomidate induced myoclonus after pre-treatment, incidence and severity of pain on etomidate injection and postoperative complications like nausea vomiting, thrombophlebitis after etomidate anaesthesia if any.

Material and Methods

A prospective, observational study was conducted on 30 ASA Class 1 and 2 adult patients of either sex undergoing elective surgical procedures under general anaesthesia necessitating endotracheal intubation. After thorough pre anaesthetic check up patients with following problems were excluded from the study:

- Patients with anticipated difficult intubation assessed by using Mallampati grading.
- Patients of known case of epilepsy or with past history of episodes of convulsion.
- Raised intracranial and/or raised intraocular pressure.
- History of allergy to lipid emulsion.
- Open globe injury.

The patients receive pre-treatment with midazolam 0.015 mg/kg iv. All the patients were give nalprazolam 0.25 mg per oral night before surgery. On the day of surgery premedication was given with inj. Glycopyrrolate 0.2 mg intramuscular 30 minutes before surgery. In the operation theatre monitors were attached and baseline vital parameters inthe form of pulse, systolic blood pressure, diastolic blood pressure, mean blood pressure and SpO_2 were recorded. Then pre-treatment drug inj. midazolam 0.015 mg/kg was injected. Ninety seconds after giving study drug patients were induced with injetomidate 0.3 mg/kg intravenously and Rocuronium 0.9 mg/kg intravenously. After giving 2-3 ml of Etomidate patients were assessed for pain on injection. Onset time of appearing myoclonic movements after completion of etomidate injection and total duration of myoclonus was also noted. Vital parameters in the form of pulse, systolic blood pressure, diastolic blood pressure, mean blood pressure and SpO_2 were recorded before pre-treatment (baseline), after pre-treatment, after induction and 1,3 and 5 minutes after intubation. Anaesthesia was maintainted with conventional methods. Postoperatively patients were assessed for side effects like nausea, vomiting, thrombophlebitis for 24 hours.

Results

All the patients studied were adults. The mean

age was 32 ± 8.23 years, the mean weight was 50 ± 7.18 kg and there were 11 male patients and 19 female patients.

The mean pulse rate at baseline was 87 ± 16.36. Mean pulse rate after giving pre-treatment, after giving etomidate and 1, 3, 5 minutes after intubation was documented. It was noted that after pre-treatment there was no change inmean pulse rate but it increased significantly after etomidate ($p < 0.05$). Pulse rate increased significantly at 1, 3, 5 minutes after intubation.

The mean systolic blood pressure before pre-treatment was 116 ± 8.46 mmHg Mean systolic blood pressure after pre-treatment, after etomidate and 1, 3, 5 minutes after intubation was documented. Mean systolic blood pressure after pre-treatment and after etomidate was not significantly different from baseline while there was increase in mean systolic blood pressure after intubation and the difference was statistically significant ($p<0.05$) at 1 and 3 minutes whereas it was not significantly different at 5 minutes.

SpO_2 did not fall before pre-treatment, after pre-treatment, after giving etomidate, and 1 minute, 3 minute and 5 minutes after intubation.

Myoclonus developed in 7 patients (23.33%). Mean time of onset of myoclonus was 13 ± 8.96 seconds. Mean duration of myoclonus was 21 ± 17.96 seconds. 3 patients had grade 1 and 4 patients had grade 2 myoclonus. No patient developed complications like nausea, vomiting, thrombophlebitis for 24 hours in the postoperative period.

Discussion

Etomidate is an anaesthetic induction agent in the clinical practice which is characterized by rapid onset, very few side effects on cardiovascular and respiratory functions as well as minimum histamine release.

For short term procedures requiring general anaesthesia, rapid clearance of the anaesthetic is desirable. Etomidate, because of its minimal respiratory side effects and favourable haemodynamic profile, is a common choice for shortterm procedures, especially in the haemodynamically compromised patients. Two undesirable side effects of etomidate are pain on injection and myoclonus. Although the problem of pain on injection has been solved by a new lipid formulation for etomidate as previous studies say, the problem of etomidate induced myoclonus, has yet to be solved.

This study was conducted in 30 adult ASA- class I and II patients of either sex undergoing elective surgery under general anaesthesia necessitating endotracheal intubation.

After thorough preanaesthesia check-up any patient with any contraindication to use etomidate were excluded from the study like history of allergy to lipid emulsion, history of epilepsy or any episode of focal or generalised convulsion, patients with increased intracranial and/or intraocular pressure, open globeinjury. Patients with anticipated difficult airway assessed by Mallampatti's grading were also excluded from the study.

In this study haemodynamic response to laryngoscopy and intubation in was studied. Difficult intubation can affect the duration of laryngoscopy and duration of the laryngoscopy is the major determining factor for haemodynamic response.

All patients were given tablet Alprazolam 0.25 mg night before surgery Premedication was given with inj. Glycopyrrolate 0.2mg intramuscular 30 minutes before surgery.

The study was to observe the effect of midazolam on etomidate induced myoclonus. Any other benzodiazepine or opioid if used in premedication might affect the result of study so only glycopyrrolate was usedas premedication.

Myoclonus is defined as an involuntary short contraction of some muscle fibresor a whole muscle, or different muscles of one group, leading to a short observable movement of the corresponding body part not longer than 100 ms.

Aissaoui Y *et al.* investigated the influence of pre-treatment with a low dose of etomidate on etomidate induced myoclonus, 87% patients in control group developed myoclonic movements [9].

Choi JM *et al.* compared the effect ofpre-treatment with low dose of rocuronium (0.06 mg/kg) on the occurrence of etomidate-induced myoclonus with control group and found that 63% patientsin control group had myoclonus [10].

Mizrak A *et al.* found the incidence of etomidate induced myoclonus was 64% in control group [11].

It was observed in various studies that incidence of myoclonus is 50-80% inetomidate anaesthesia when no pre-treatment agent has been given. Keeping in mind such a high incidence of myoclonus (50-80%) control group was not taken in our study.

Schwarzkopf KR *et al.* studied effect of pre-treatment with etomidate 0.05 mg/kg IV and midazolam 0.015 mg/kg IV onetomidate induced

myoclonic muscle movements which was compared with placebo in a randomized double-blind study [12].

Huter Lars *et al.* studied the effect of 0.015 mg/kg IV Midazolam on Etomidate induced myoclonus, which was administered 90 seconds before induction of anaesthesia with etomidate 0.3 mg/kg iv [4].

Ideally, a pre-treatment drug for preventing myoclonic movements should beshort acting, not have significant effects on respiration and haemodynamics, andnot prolong recovery from anaesthesia especially in short term procedures.

Therefore, a low dose of midazolam 0.015 mg/kg IV was selected in our study for evaluation.

Etomidate is attractive for short term anaesthesia because it allows early recovery and relative cardiovascular stability. Hence, for short lasting procedures, any co-medication given for anaesthetic or sedative purpose or toreduce myoclonus should not interfere with this favourable pharmacodynamic profile.

Although opioids have been shown to reduce myoclonus, administration of opioid like high doses of fentanyl may be undesirable for short-term procedures because of potential respiratory depression. High doses of fentanyl are also associated with apnea.

After proper preoxygenation baseline pulse, systolic, diastolic blood pressure were taken. Then pre-treatment drug was injected. After giving pre-treatment drug pulse, blood pressure, and SpO_2 were recorded. After ninety seconds of giving pre-treatment drug, patients were induced with inj. etomidate 0.3 mg/kg IV and vital parameters were recorded.

Pain on injection is one of the all bothersome side effects of etomidate [13]. Pain on injection was graded as [7]:

- Grade 1 - Mild (pain reported only in response to questioning and without any behavioral sign).
- Grade 2 - Moderate pain (pain reported in response to questioning and accompanied by behavioural sign or pain reported spontaneously without questioning).
- Grade 3 - Severe pain (strong vocal response or response accompanied byfacial grimacing, arm withdrawal).

Y. Nyman *et al.* found a significantly lower incidence of injection pain in the Etomidate-Lipurogroup as compared with the Propofol-Lidocaine group (5.0% Vs 47.5%, $p<0.05$) [14].

Pain on injection has been a problem with etomidate induction like other anaesthetic agents like propofol. Pain on injection is specially not acceptable in children.

Like propofol and other general anaesthetics, etomidate at high concentration activates transient receptor potential type A-1 channels, a mechanism that mayunderlie pain during injection. Transient receptor potential type A-1 channels are involved in inflammation and pain sensation. But in our study, a new lipid formulation of etomidate was used. In this new lipid formulation, etomidate is dissolved in a fat emulsion of medium and long chain triglycerides. Therefore, with Etomidate-Lipuro side effect of pain oninjection has almost gone making it a suitable induction agent for anaesthesia.

After complete injection of etomidate, inj Rocuronium 0.9 mg/kg IV was given to facilitate endotracheal intubation and isoflurane (0.8%) or halothane (0.5%)was started.

Succinylcholine is the most commonly used agent to facilitate endotracheal intubation. It is associated with fasciculations. Succinylcholine induced fasciculations could have been difficult to differentiate from etomidate induced myoclonus so succinylcholine was avoided and rocuronium was the agent used for endotracheal intubation.

After etomidate injection patients were observed for myoclonus. Myoclonus was graded as [4]:

- Grade 0 - No myoclonus.
- Grade 1 - Mild myoclonus (only mild fasciculation involving face and/ordistal upper and /or lower extremities).
- Grade 2 - Moderate myoclonus (marked movements of the face and /orlimbs).
- Grade 3 - Severe myoclonus (involving limbs and trunk).

Schwarzkopf KR *et al.* found a significantly low incidence (20%) of etomidate induced myoclonus in midazolam group (0.015 mg/kg IV) given as pre-treatment compared to placebo group (90%) [12].

Lars Huter *et al.* found that incidence of etomidate induced myoclonus in midazolam pretreated group (0.015 mg/kg IV) was 10% compared to 50% incidence in control group [4].

The incidence of myoclonus in midazolam pretreated group in present study was similar to above mentioned study.

Do *et al.* studied the effect of injectionrate on etomidate-induced myoclonus. In the fast injection group 28% (7/25) of the patients showed myoclonus of a severe grade. In contrast, only 4% (125) of the patients showed severe myoclonus in slow injection group [15].

The neurologic mechanism of myoclonus is a disinhibition phenomenon of subcortical structure. That is etomidate depresses cortical activity before it depresses subcortical activity, thus depresses the neural circuits prior to excitatory circuits and not caused by an epileptic focus.

Benzodiazepines prevent myoclonus by inhibiting subcortical neuronal activity. The different effects of benzodiazepines on the different GAB Areceptors also explain the mechanism by which these drugs reduce the incidence of myoclonic movements.

Time of onset of appearing myoclonic movements after etomidate injection wasalso recorded in present study. Mean time of onset of myoclonus was 13 ± 8.96 seconds.

Much literature is not available about the effect of pre-treatment on the onset and duration of etomidate induced myoclonus. Only one study noted that pre-treatment with remifentanil reduces the duration of myoclonus. Larger studies are required to further evaluatethe effect of midazolam on characteristics of etomidate induced myoclonus.

Conclusion

Midazolam is a good pre-treatment option before induction with etomidate. Midazolam pre-treatment resulted in reduced incidence and severity of etomidate induced myoclonus. It did not result in any significant adverse effect of the vital parameters and did not result in any nausea, vomiting and thrombophlebitis in the post-operative period.

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