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A double blind randomized controlled study to evaluate the effect of dexmedetomidine in prevention of myoclonus occurring due to etomidate induction

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Abstract

Etomidate is a popular intravenous induction agent because it has a stable haemodynamic profile and results in minimal histamine release. Myoclonus is observed in 50%–80% of patients who did not receive pretreatment before etomidate administration, which increases the risk of regurgitation and aspiration in emergency conditions. Various drugs were used in the treatment of myoclonus but the results have been inconclusive. Dexmedetomidine, a new alpha-2 agonist has been tried by several authors to suppress the myoclonus induced by etomidate. A prospective randomized controlled double blind study was conducted in seventy patients aged between 18-55 years belonging to ASA I and II scheduled for elective surgery under general anaesthesia. After obtaining informed written consent, a detailed preanaesthetic evaluation was done and investigations were obtained as indicated. The patients were randomized into 2 groups with 35 patients each, received either 0.5 μg/kg of dexmedetomidine in 10 ml saline (Group D) or 10 ml of Saline (Group S) over a period of 10 minutes prior to etomidate induction. The incidence of severe myoclonus was significantly less in group D compared to saline group with p = 0.031 (8.57% in group D and 28.5% in group S). However there was no change in the incidence of myoclonus (P = 0.237) and pain on injection (p = 0.309) in both groups. Recovery profile was comparable in both groups. Our study shows that pretreatment with dexmedetomidine 0.5 μg/kg IV is effective in reducing the severity of etomidate induced myoclonic muscle movements without however dexmedetomidine does not have any significant effect on the incidence of myoclonus following etomidate induction.

Keywords: Etomidate, dexmedetomidine, myoclonus

Introduction

The discovery of IV anaesthetics has long been an important milestone in the development of anaesthesia. Prior to this, induction of general anaesthesia necessarily required inhalation of gases or

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vapour which was an unpleasant experience to most of the patients.
Etomidate is a carboxylated imidazole drug used for induction of general anaesthesia and sedation was introduced into clinical practice in 1973. Etomidate is a popular anaesthetic induction agent because it

has a stable haemodynamic profile and results in minimal histamine release. Previous studies reported that at 0.3 mg/kg induction doses, etomidate does not cause significant alterations in heart rate, systolic, diastolic, and mean arterial pressures, right atrial pressure, systemic and pulmonary vascular resistance, stroke volume, cardiac index, systemic blood flow, and shunt flow in pediatric patients undergoing congenital cardiac shunt surgery and in adults [1].
Two undesirable side effects of etomidate are pain on injection and myoclonus. Pain on injection, venous irritation and haemolysis have been abolished by a new fat emulsion of etomidate (medium chain triglyceride and soya bean named etomidate- lipuro, Germany) but the new solvent has not reduced the incidence of myoclonus after etomidate injection.
The induction dose of etomidate is 0.2 to 0.4 mg/kg. Myoclonus is observed in 50% – 80% of patients who did not receive pretreatment before etomidate administration. Involuntary myoclonic movements are common during the induction period as a result of subcortical disinhibition and are unrelated to cortical seizure activity [2].
Myoclonus may be of clinical significance in a variety of patients undergoing induction of general anaesthesia. In theory, in emergency conditions, the myoclonus may increase the risk of regurgitation and aspiration. As a result of high intraocular pressure, myoclonus might increase the risk of vitreous prolapse after an open globe injury. In the case of electric cardioversion; continuous electrocardiogram (ECG) recordings may be disturbed due to the patient's myoclonic movements [3].
Although the mechanism of etomidate induced myoclonus is still not clear, a number of drugs have been investigated for their ability to suppress these myoclonic movements. Opioids such as fentanyl, sufentanil and remifentanil, benzodiazepines, magnesium sulfate, low dose etomidate and rocuronium have been shown to reduce myoclonus to some extent. But even with these drugs, myoclonus was still observed at a rate of 7%-50% [4].
The carboxylated imidazole etomidate exhibits structural similarities to specific alpha-2 adrenoceptor agonists that belong to the class of imidazole compounds, such as clonidine and dexmedetomidine. Besides the chemical structure, etomidate and alpha-2 adrenoceptor agonists share some clinical similarities, such as inducing sedation/hypnosis with high cardiovascular stability and only minor respiratory depression. Dexmedetomidine has been tried by several authors to suppress the myoclonus induced by Etomidate [5].
Although the mechanism of etomidate-induced myoclonus is still not clear, a number of drugs have been investigated for their ability to suppress these myoclonic movements. Pretreatment with benzodiazepines opioids and rocuronium have been shown to reduce myoclonus to some extent. Dexmedetomidine is a strong, highly selective α2-adrenoceptor agonist with a wide spectrum of pharmacological properties. It provides sedation, anxiolysis, and hypnosis, as well as analgesia, and has sympatholytic properties. However, few studies have evaluated the effects of Dexmedetomidine on myoclonus after etomidate injection. This study aimed to investigate the effects of Dexmedetomidine pretreatment on the incidence and severity of myoclonus during anesthesia induction with etomidate providing the same hemodynamic and cardiostability [6].
Thus the present clinical study was undertaken to investigate the effects of pretreatment with dexmedetomidine on the incidence and severity of myoclonus and injection pain during induction of general anaesthesia with etomidate providing good hemodynamic and cardiostability in elective surgery patients.

Methodology
Source of data
Design of study

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Prospective, randomized control trial, double blind study.

Sample size and sampling method

The incidence of myoclonus in the non-pretreatment group was estimated to be 70% based on previous studies. Keeping power at 80% and confidence interval at 95% to detect 50% reduction in the incidence of myoclonus in the pretreatment group, the minimal sample size required is 32 patients in each group. For better validation, 35 patients were randomized in each group. Randomization is done using numbers generated from www.randomisation.org.

Inclusion criteria

1. Patients aged between 18-55 yrs.
2. Patient who gave informed written consent (annexure 1).
3. ASA physical status I and II patients (annexure 2).

Exclusion criteria

1. Patients with cardiovascular and respiratory diseases.
2. Patients with chronic abuse of alcohol, drugs, psychotropic agents.
3. Patients with hepatic, renal diseases and epilepsy.
4. Patients with adrenal disease.
5. Patients who are pregnant and lactating.

Pre-anaesthetic evaluation & preparation

A thorough pre-anaesthetic check-up was done for all patients a day before surgery. No special investigations were required pertaining to study. Preoperative investigations including complete blood count (CBC), urine examination, blood sugar, serum electrolytes, coagulation profile, liver and renal function tests, electrocardiography and echocardiography, chest x-ray were obtained as indicated. They were advised to fast from night before the day of surgery. Premedication with oral ranitidine hydrochloride 150 mg and alprazolam 0.25 mg were given the night before surgery.

Preparation in operation theatre

Anaesthesia workstation was checked. Appropriate size endotracheal tubes, working laryngoscope with medium and large sized blades, stylet and working suction apparatus were kept ready before the induction of general anaesthesia. Emergency drug tray consisting of atropine, adrenaline and mephentermine were also kept ready for any eventuality.
After obtaining informed written consent from the patients, participation consent and surgeon's consent, the patients were randomly divided into two groups.
Group D: Dexmedetomidine (n = 35).
Group S: Saline (n = 35).

Patients on arriving to operation theatre, IV cannulation was done with 18 G cannula and ringer lactate was connected. Patients were connected to monitors such as ECG, noninvasive blood pressure, pulse oximetry and entropy. The patients were premedicated with IV 50 mg of Inj. ranitidine and 0.2 mg of Inj. glycopyrrolate. The study drug syringes were prepared by an anaesthetist not involved in the observation. Patients in group D received 0.5 μg/kg of Inj. dexmedetomidine in 10 ml saline and group S received 10 ml of Saline over a period of 10 minutes. Oxygen supplementation through mask was given during this period. Ramsay Sedation Score was noted at baseline, 5^{th} and 10^{th} minute during infusion (annexure 3). Etomidate 0.3 mg/kg was administered over 30 seconds and pain related with

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injection was

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evaluated; 0: no pain, 1: mild pain, 2: moderate pain, 3: severe pain (annexure 4). Also myoclonus was observed for two minutes following etomidate induction and graded; 0: no myoclonus, 1: mild myoclonus, 2: moderate myoclonus, 3: severe myoclonus (annexure 5). Two minutes after etomidate injection, Inj. midazolam 0.02 mg/kg, Inj. fentanyl 2 μg/kg and Inj. atracurium 0.5 mg/kg was administered. After three minutes, patients were intubated with appropriate sized cuffed oral endotracheal tube. Anaesthesia was maintained according to institutional protocol with N_2O + O_2 +sevoflurane. Hypotension, defined as more than 20% decrease in mean arterial pressure, was treated with fluid boluses and injection ephedrine 6 mg IV. Bradycardia, defined as heart rate less than 50 beats/min, was treated with injection atropine 0.6 mg IV. At the end of surgery, residual paralysis was reversed with 0.05 mg/kg of Inj. neostigmine and 0.01 mg/kg of Inj. glycopyrrolate. At the time of extubation, recovery profile was noted (the time between cut off of inhalational agent to the opening of eyes) and extubation time (the time between cut off of inhalational agent to removal of endotracheal tube) was recorded. Ramsay sedation score after extubation was recorded.

Results

Table 1: Age distribution of patients.

Age in years	Group D		Group S	
	No	%	No	%
<= 20	1	2.8	2	5.7
21 – 30	10	28.6	4	11.4
31 – 40	13	37.1	14	40
41 – 50	10	28.6	14	40
51 – 60	1	2.9	1	2.9
Total	35	100.0	35	100.0
Mean ± SD	36.4 ± 8.7		37.69 ± 8.13	

The mean age was 36.4 ± 8.7 years in Group D and 37.69 ± 8.13 years in Group S which was comparable.

Table 2: Diagnosis distribution of patients studied.

Surgeries	Group D		Group S	
	No	%	No	%
Head and Neck surgeries	10	28.6	19	54.3
Upper abdominal surgeries	4	11.4	3	8.6
Breast surgeries	8	22.9	3	8.6
Laparoscopic surgeries	9	25.7	9	25.7
Others	4	11.4	1	2.8
Total	35	100.0	35	100.0

Types of surgeries were uniformly distributed in both the group and were comparable.

Table 3: Comparison of duration of surgery between the groups.

	Group D (min)	Group S (min)	p value
Duration of surgery in min	67.57±16.91	70.57±16.57	0.471

The mean duration of surgery was 67.57±16.91 minutes in group D and 70.57±16.57 minutes in group S which was comparable with p = 0.471.

Table 4: Pain on injection of patients studied.

Pain grading	Group		p value
	Dexmedetomidine (D)	Saline (S)	
No pain	32 (91.42%)	30 (85.71%)	0.309
Mild pain	2 (5.71%)	5 (14.28%)	
Moderate pain	1 (2.85%)	0 (0%)	
Severe pain	0 (0%)	0 (0%)	

32 patients in group D (91.42%) and 30 patients in group S (85.71%) experienced no pain on injection following etomidate induction. 2 patients in group D (5.71%) and 5 patients in group S (14.28%) had mild pain on injection while 1 patient in group D (2.85%) had moderate pain on injection. Thus there was no statistically significance on comparing incidence of pain on injection in both the studied groups ($p = 0.309$).

Table 5: Myoclonus in two groups of patients studied.

Myoclonus grading	Group		p value
	Dexmedetomidine (D)	Saline (S)	
No myoclonus	20 (57.14%)	16 (45.71%)	0.237
Mild myoclonus	6 (17.14%)	4 (11.42%)	0.367
Moderate myoclonus	6 (17.14%)	5 (14.28%)	0.5
Severe myoclonus	3 (8.57%)	10 (28.5%)	0.031*
Total incidence of myoclonus	15 (42.86%)	19 (54.29%)	0.237

20 patients in group D (57.14%) and 16 patients in group S (45.71%) had no myoclonus following etomidate induction which was statistically insignificant ($p = 0.237$). 15 patients (42.86%) in group D and 19 patients (54.29%) in group S had myoclonus of varying severity following etomidate induction. Overall incidence was statistically not significant ($p = 0.237$).

6 patients in group D (17.14%) and 4 patients in group S (11.42%) experienced mild myoclonus ($p = 0.367$). 6 patients in group D (17.14%) and 5 patients in group S (14.28%) had moderate myoclonus ($p = 0.5$) following etomidate induction which was statistically insignificant. 3 patients in group D (8.57%) and 10 patients (28.5%) in group S had severe myoclonus following etomidate induction which was statistically significant with $p = 0.031$.

Table 6: Time taken for loss of palpebral reflex/ loss of verbal commands of patients studied.

	Group	Mean (seconds)	Standard deviation	p value by 't' test
Loss of palpebral reflex	Dexmedetomidine	41.14	9.17	0.21
	Saline	43.57	6.72	
Loss of verbal commands	Dexmedetomidine	41.14	9.17	0.22
	Saline	43.51	6.68	

The mean loss of palpebral reflex following etomidate induction was 41.14 ± 9.17 seconds in group D and 43.57 ± 6.72 seconds in group S which was statistically insignificant ($p = 0.21$).

The mean loss of verbal commands following etomidate induction was 41.14 ± 9.17 seconds in group D and 43.51 ± 6.68 seconds in group S which was statistically insignificant ($p = 0.22$).

Table 7: Comparison of time to eye opening, time to extubation.

	Group	Mean (min)	Standard deviation	p value by 't' test
Time to extubation	Dexmedetomidine	11.89	2.54	0.298
	Saline	12.57	2.91	
Time to eye opening	Dexmedetomidine	10.60	2.58	0.252
	Saline	11.34	2.80	

Mean time to extubation from stopping of inhalational agent was 11.89 ± 2.54 minutes in group D and 12.57 ± 2.91 minutes in group S which was statistically not significant (p = 0.298). Mean time to eye opening from the stopping of inhalational agent was 10.60 ± 2.58 minutes in group D and 11.34 ± 2.80 minutes in group S which was statistically not significant (p = 0.252).

Discussion

Etomidate is widely used as an anaesthetic 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 two side effects, pain on injection and myoclonus. Etomidate is weak water soluble since it is formulated with propylene glycol, lipid emulsions, and polyethylene and phosphate buffers. Due to this formulation, it causes pain and inflammation and sometimes phlebitis and thrombosis at the injection site. Pain on injection has been largely eliminated by use of a lipid formulation of etomidate, but myoclonus remains a common problem during anaesthesia induction. Etomidate induced myoclonus can have serious consequences, such as vitreous prolapse in a patient with open eye injury and ECG leads may become detached during myoclonic movements. Decreased oxygen saturation, as measured by pulse oximetry has been reported.

Several studies have reported myoclonic activity in 50% to 80% of patients receiving etomidate. Though various drugs have been tried to reduce the incidence of myoclonic movements after etomidate administration, the mechanism by which this effect is achieved remains unclear. Doenicke *et al*. reported that myoclonus after etomidate is caused by subcortical disinhibition [7]. Etomidate interacts with GABA-A receptors suppressing the central nervous reticular activating system. With interruption of GABA neurons, pathways associated with skeletal muscle control can become more sensitive, allowing spontaneous nerve transmissions to occur. These events can ultimately lead to myoclonic muscle contractions.

Many drugs have been reported to prevent myoclonus associated with etomidate. Schwarzkopf *et al*. observed decreased myoclonic incidence by 20% after intravenous administration of 0.015 mg/kg midazolam when given 90 minutes prior to etomidate administration. However, intravenous midazolam injection could induce respiratory depression and sedation. In a study conducted by Nevriye Salman *et al*., they observed that 0.05 mg/kg midazolam given by intramuscular route 30 minutes before etomidate administration did not decrease myoclonus incidence. It was suggested that the varying effects of midazolam was due to different dose regimens and timing. It was also reported that despite the low cardiovascular depressant effects, midazolam has respiratory depressant and sedation effects which are the major disadvantages [8]. Hwang *et al*. compared the effects of midazolam 0.5 mg/kg with remifentanil 1μg/kg on myoclonic movement following etomidate injection and documented that 0.5 mg/kg midazolam decreased incidence of myoclonus associated with etomidate and was a better alternative than remifentanyl in patients with low cardiac reserve [9].

Stockam *et al*. revealed that 100 μg fentanyl did not decrease myoclonus incidence; higher doses decreased myoclonic activity, but caused apnea [10]. Canessa *et al*. used fentanyl and alfentanyl and documented that both agents decreased myoclonus associated with etomidate, but caused respiratory depression [11]. Kelsaka *et al*. stated that remifentanil as a short acting opioid is effective in prevention

of myoclonus but can cause severe bradycardia and chest rigidity [12]. Choi *et al*. reported that pretreatment with rocuronium significantly reduced the frequency of myoclonus after etomidate injection by blocking transmission at the neuromuscular junction; However, it was accompanied with some disadvantages associated with muscle relaxants such as airway obstruction, regurgitation, and aspiration. An ideal drug for preventing myoclonus should be short acting, not produce significant respiratory depression or haemodynamics and not prolong recovery from anaesthesia.

Dexmedetomidine has been tried as an alternative drug in the prevention of myoclonus following etomidate induction. Dexmedetomidine is a selective, potent α-2 adrenoceptor agonist and has analgesic and anxiolytic activity. Guler *et al*. did not observe haemodynamic effects following 0.5 μg/kg intravenous bolus dexmedetomidine [13]. Previous studies showed that dexmedetomidine used as a premedicant at doses of 0.5-1 μg/kg had sedative and anaesthetic sparing effects, as well as attenuating airway/circulatory reflexes during anaesthesia. So in our study, we used 0.5 μg/kg dexmedetomidine IV as pretreatment before etomidate induction.

In a study conducted by Salman N *et al*. it was observed that pretreatment with dexmedetomidine 0.5 μg/kg and midazolam 0.25 mg/kg decreased myoclonus associated with etomidate use. In their study, severe myoclonus was not observed in both groups, only mild myoclonus was more common in dexmedetomidine group (16.7% vs 40%) (p<0.05) [8].

In a study conducted by Sema Aktolga *et al*. it was observed that pretreatment with midazolam 0.5 mg/kg and dexmedetomidine 1 μg/kg reduced the incidence and the severity of myoclonic movements after etomidate induction (p = 0.000).19 (37%) of patients in the midazolam group M, 15 (30%) of patients in the dexmedetomidine group D and 46 (90%) of patients in the placebo group P developed myoclonic movements within 60 seconds after induction with etomidate [14].

Mizrak *et al*. in their study reported that both 0.5 μg/kg dexmedetomidine and 1mg/kg thiopental was effective in reducing the incidence and severity of etomidate induced myoclonic muscle movements. In their study the incidence of myoclonus was 34% in dexmedetomidine group, 37% in thiopentone group, 64% in saline group. The incidence of severe myoclonic movements was 30% in saline group, 13% in dexmedetomidine group, 13% in thiopental group (p<0.05) [15].

H.F. Luan *et al*. in their study compared two doses of dexmedetomidine, 0.5 (group II) and 1.0 μg/kg (group III) with saline group (group I) in which the incidence of myoclonus was significantly reduced in groups II and III (30% and 36.7%), compared with group I (63.3%) (p<0.05). However, there were no significant differences in the severity of myoclonus among the 3 groups [16].

In the present study, 20 patients in group D (57.14%) and 16 patients in group S (45.71%) had no myoclonus following etomidate induction which was statistically insignificant (p = 0.237). 15 patients (42.86%) in group D and 19 patients (54.29%) in group S had myoclonus following etomidate induction which was statistically not significant (p = 0.237). Out of them 6 patients in group D (17.14%) and 4 patients in group S (11.42%) experienced mild myoclonus (p = 0.367), 6 patients in group D (17.14%) and 5 patients in group S (14.28%) had moderate myoclonus (p = 0.5) which was statistically insignificant. Incidence of severe myoclonus was significantly lower in group D compared to group S. Only 3patients in group D (8.57%) had severe myoclonus compared to 10 patients (28.5%) in group S (p = 0.031). Thus the severity of myoclonus was significantly reduced by dexmedetomidine which was consistent with the other studies. However unlike the other studies, there was no change in the incidence of myoclonus following etomidate induction.

In a study conducted by Salman N *et al*. the pain on injection was significantly less in midazolam group compared to dexmedetomidine group following etomidate induction; no pain; p< 0.001, mild pain; p = 0.005, moderate pain; p = 0.002, severe pain; p<0.001 [8].

In a study conducted by Sema Aktolga *et al*. pretreatment with midazolam 0.5 mg/kg and dexmedetomidine 1 μg/kg reduced the incidence of injection pain after etomidate induction (p = 0.000). 2% of patients in the group M, 6% of patients in the group D and 85% in the placebo group P developed pain on injection within 60 seconds after induction with etomidate [14].

In contrast to above studies, in our study the incidence of pain on injection was less in both the study

groups, 32 patients in group D (91.42%) and 30 patients in group S (85.71%) did not have any pain on injection following etomidate induction (p = 0.309). 2 patients in group D (5.71%) and 5 patients in group S (14.28%) had mild pain on injection while 1 patient in group D (2.85%) had moderate pain on injection. This may be because we had used lipid formulation of etomidate (lipuro, Germany).

Sema Aktolga *et al*. in their study observed that the loss of the eyelash reflex occurred d at 69 ± 30.4 seconds in placebo group and 40.8 ± 35.4 seconds in dexmedetomidine group after the administration of etomidate ($p< 0.05$) [14].

In the present study, the mean loss of palpebral reflex following etomidate induction was 41.14 ± 9.17 seconds in group D which was similar to Sema Aktolga *et al* observation. Unlike them, we did not find any delay in induction in group S (43.57 ± 6.72 second). However, it is possible that patients might be in lighter planes of anaesthesia or sedation could have been deep, that they did not response to the request.[17] This clinical assessment of depth of anaesthesia is ambiguous and does not have high sensitivity or specificity.

Sema Aktolga *et al*. in their study observed decrease in BIS values after pretreatment with midazolam and dexmedetomidine [14]. In our study, we used entropy to measure the depth of anaesthesia. Entropy is a useful tool to quantify anaesthetic drug effect and is comparable to established processed EEG parameters like BIS. There was significant fall in RE (p = 0.007) and SE (p = 0.006) values from the baseline in dexmedetomidine group compared to saline group at the end of dexmedetomidine infusion which was consistent with Sema Aktolga observation. In a study conducted by Duncan *et al*. they concluded that entropy is a reliable technique with high sensitivity and specificity for monitoring depth of anaesthesia [18]. In our study, we observed that the time to achieve Entropy 50 was 64.23 ± 9.67 seconds in group D compared to 71.46 ± 15.76 seconds in group S. This showed that pretreatment with dexmedetomidine led to rapid induction of anaesthesia (p = 0.02).

Conclusion

In conclusion, our study shows that pretreatment with dexmedetomidine 0.5 μg/kg IV is effective in reducing the severity of etomidate induced myoclonic muscle movements without any haemodynamic side effects. However dexmedetomidine does not have any significant effect on the incidence of myoclonus following etomidate induction.

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