Comparison of Dexmedetomedine with Fentanyl for Prevention of Etomidate Induced Myoclonus

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ABSTRACT
Background & Aims: Etomidate has a stable cardiac profile as an induction agent. But, reported incidence of etomidate induced myoclonus is 50% to 80%. This study was conducted to compare the effect of dexmedetomidine with fentanyl for reduction of etomidate induced myoclonus. **Materials and Method:** This study was conducted in 60 ASA grade I,II,III patients in the age group of 18-55 years undergoing elective surgeries under general anaesthesia. Patients were randomized and divided into 2 groups of 30 patients each. Group 1 received Inj. dexmedetomidine 0.5 mcg /kg iv and Group 2 received Inj. fentanyl 1 mcg /kg iv as a premedication slowly over 5 mins. After that, they were administered Inj. etomidate 0.3 mg/kg and were observed for myoclonus for 2 minutes. Severity of etomidate induced myoclonus was assessed using four point intensity scoring. Safety of study drugs was compared using mean HR, mean BP and adverse events observed. **Results:** Myoclonus was observed in 36.67% patients after inj. dexmedetomidine 0.5 mcg /kg and in 50% patients after inj. fentanyl 1 mcg /kg (P value = 0.046). Incidence of myoclonus with grade 1,2 and 3 was 26.66%, 10% and 0% respectively in group 1 and 33.33%, 13.33% and 3.33% in group 2 respectively. **Conclusion:** Incidence of etomidate induced myoclonus was significantly decreased in patients pre-treated with dexmedetomidine in comparison with fentanyl. In terms of severity grading, difference between these two drugs was insignificant.
Keywords: Myoclonus, Etomidate, Dexmedetomidine, Fentanyl**.**

INTRODUCTION

Etomidate is a carboxylated imidazole derived sedative-hypnotic agent, acting directly on gamma-aminobutyric acid (GABA) receptor complex, blocking neuro excitation and producing anaesthesia. It demonstrates a fast onset of action and a short half-life. It shows stable cardiac profile and minimal respiratory side effects, as compared to other induction agents.[1]

Pain on injection, phlebitis, hemolysis and myoclonus are common adverse effects observed with this drug. Myoclonus is defined as sudden, brief, involuntary muscle jerks either irregular or rhythmic, and has been reported in 50 – 80% of patients.[2] The mechanism of etomidate induced myoclonus appears to be disinhibition of subcortical structure that normally suppress extra-pyramidal activity. Disruption of the cortical GABA mediated inhibition makes skeletal muscles susceptible to spontaneous nerve transmission, thereby leading to myoclonic movements.[3]

Dexmedetomidine is a strong, highly selective α2-adrenoceptor agonist with a wide spectrum of pharmacological properties. It provides sedation, anxiolysis, hypnosis, as well as analgesia and has sympatholytic properties.[4,5] Fentanyl is a synthetic opioid agonist with analgesic and anesthetic

Properties. It selectively acts on mu receptors and reduces neural excitability and produces good analgesic and anesthetic effect.[6]

Few studies have evaluated the effects of dexmedetomidine[3,4] and fentanyl[6] on myoclonus after etomidate injection. There is however, no study evaluating the comparison of effect of dexmedetomidine and fentanyl as a premedication on the incidence of etomidate induced myoclonus.

The present study was therefore conducted with an aim to compare the effect of dexmedetomidine and fentanyl on the incidence of etomidate induced myoclonus.

MATERIALS AND METHOD

This prospective, comparative, randomised interventional study was conducted in a tertiary care teaching institute from October 2022 to January 2023 after obtaining approval from the Institutional Ethics Committee (Ref No-98/2022 dated- 23/11/2022). Written and informed consent was obtained from patients aged 18-55 years of both genders with ASA Risk I-III scheduled for surgery for the study. Patients having ASA grade IV and V, patients who were allergic to dexmedetodine, fentanyl or etomidate and patients with altered coagulation profile were excluded. In pre-operative assessment, patient`s general examination, systemic examination and all required investigations including complete blood count, random blood sugar, blood urea, serum creatinine, liver function test, ECG and chest X ray were performed a day before the surgery. Patients were advised to remain nil by mouth (NBM) for 6-8 hours before the surgery.

Procedure: After arrival in the operation room, routine monitoring (ECG, pulse oximetry, non-invasive arterial blood pressure) was performed and intravenous line was secured in a suitable vein. Administration of 500 ml DNS or selective fluid of choice via peripheral access was started. Baseline vitals were recorded. Patients were given premedication in the form of inj. glycopyrrolate (4 mcg /kg) intravenously. Patients were pre-oxygenated with 100% oxygen via bain's circuit with fresh gas flow of 8 l/min. for 3-5 mins. Patients were randomized using computer generated randomised list into one of the following two equal groups: Group 1: Patients received 0.5 mcg /kg of inj. dexmedetomidine intravenously diluted in 10 ml NS over 5 min[3,4,5], Group 2: Patients received 1 mcg /kg of inj. fentanyl intravenously diluted in 10 ml NS over 5 min.[6,7] Two minutes after administering the study drug, etomidate 0.3 mg/kg iv was administered over the next 2 min and patients were monitored for myoclonus over the next 2 min. Myoclonus was defined as involuntary short muscle contractions leading to short observable movements in parts of body. Its severity was assessed using the four point intensity score[5,6]: no myoclonus, mild myoclonus (mild movements of a body segment, e.g. finger or wrist only), moderate myoclonus (mild movements of two different muscles e.g., face & mask) and severe myoclonus (-intense tonic movements in two or more muscle groups e.g., fast adduction of a limb). Depending on the time of onset, presence or absence of myoclonus in 2 min was recorded. Laryngoscopy and intubation was facilitated by giving depolarizing muscle relaxant Inj. Succinyl choline (2 mg/kg) intravenously. For maintenance, oxygen (50%), sevoflurane (1-2%) and non-depolarising muscle relaxant inj. atracurium (0.5 mg/kg) loading dose intravenously was given and thereafter 0.1 mg/kg maintenance dose intravenously was given intermittently. Intraoperative monitoring (pulse rate, non-invasive blood pressure, SpO2, EtCO2, input, output, temperature) was performed. After completion of procedure, patients were reversed from neuromuscular block with inj. Neostigmine (50 mcg /kg) intravenously premedicated with inj. glycopyrrolate (8 mcg /kg) intravenously. After oral and tracheal suction, extubation was performed after assessing the patient. Patients were monitored in the recovery room for pulse, blood pressure (SBP, DBP), temperature and oxygen saturation.

Sample size was calculated based on a previous study by Luan et al.[5], who observed that the incidence of myoclonus with 0.5 mcg /kg dexmedetomidine was 36.7%. To detect an inferiority margin with a difference of 0.35 in the incidence of myoclonus between 0.5 mcg /kg dexmedetomidine and 1 mcg /kg of fentanyl, the minimum required sample size with 80% power of the study and 5% level of significance was 28 patients in each study group. To reduce the margin of error, the total sample size was kept as 60 patients.

Data were tabulated and statistical analysis was performed. Continuous data such as patient`s age and weight were expressed as mean ± standard deviation, whereas categorical data such as sex and incidence of myoclonus, were expressed as frequencies (percentages). Data were analyzed using student t-test and Pearson Chi-square test for continuous and categorical variables, respectively. $P < 0.05$ was considered as statistically significant.

RESULTS

Sixty-five patients were assessed for eligibility and sixty patients were randomly allocated to two study groups (Figure 1). Demographic parameters were comparable in both groups, with no statistically significant difference (Table 1). Male to female ratio in groups 1 and 2 were 18:12 and 19:11 respectively. No myoclonus was observed in 63.33% patients after inj. dexmedetomidine 0.5 mcg /kg in Group 1 and in 50% patients after inj. fentanyl 1 mcg /kg in Group 2 (P value = 0.046). Myoclonus with severity grade 1, 2 and 3 was 26.66%, 10% and 0% respectively in group 1.

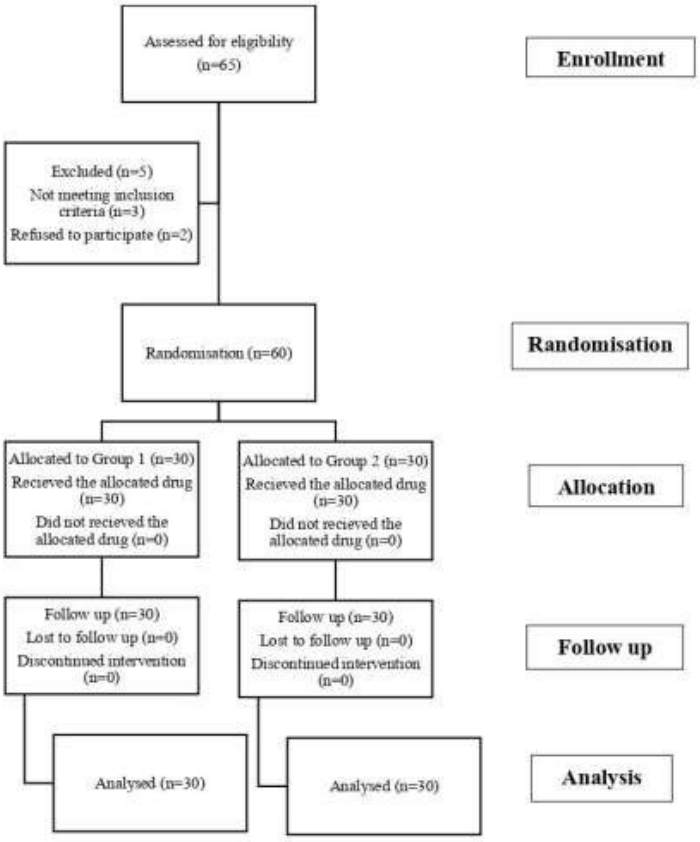

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Myoclonus with severity grade 1, 2 and 3 was 33.33%, 13.33% and 3.33% in group 2 respectively. Difference in severity grading of myoclonus among the two groups was not statistically significant (Table 2). Mean pulse rate and Mean arterial pressure of the two groups were comparable at all time points (Tables 3 &4). There was no statistically significant difference in the incidence ofintraoperative side effects like bradycardia, hypotension, tachycardia, and hypertension among the two groups (Table 5).

Table 1: Baseline characteristics of enrolled patients

Parameters	Group 1 (n=30)	Group 2 (n=30)	P value
Age in years (Mean ± SD)	34.27±9.56	34.30±9.63	0.99
Weight in kg (Mean ± SD)	63.4±8.63	67.57±9.57	0.082

Table 2: Incidence and severity of Etomidate Induced Myoclonus (EIM)

Myoclonus-grading	Group 1 (n=30)		Group 2 (n=30)		P value
	No.	%	No.	%	
0	19	63.33%	15	50%	0.046
1	8	26.66%	10	33.33%	0.217
2	3	10%	4	13.33%	0.516
3	0	0%	1	3.33%	0.081

Table 3: Comparison of changes in mean Pulse Rate (PR) between two groups

Pulse rate	Group 1 (n=30)	Group 2 (n=30)	P value
	Mean ± SD	Mean ± SD	
At 0 min	87.67±12.92	85.80±12.46	0.57
At 5 min	86.80±16.51	93.93±15.76	0.092
At 10 min	85.60±12.20	88.53±12.48	0.36
At 15 min	83.73±9.32	85.40±11.35	0.53
At 20 min	83.00±10.26	82.93±10.38	0.97
At 25 min	83.53±7.77	83.73±11.08	0.93

Table 4: Mean Arterial Pressure (MAP) in study groups at various intervals

Mean Arterial Pressur	Group 1 (n=30)	Group 2 (n=30)	P value
	Mean ± SD	Mean ± SD	
At 0 min	94.3±6.78	92.9±7.59	0.45
At 5 min	93.53±9.88	98.53±9.84	0.05
At 10 min	91.00±7.11	93.9±6.58	0.11
At 15 min	91.77±7.12	90.43±6.08	0.43
At 20 min	92.23±5.85	90.23±7.03	0.23
At 25 min	91.37±5.57	90.27±6.90	0.50

Table 5: Intraoperative side effects observed in patients

Side effects	Group 1 (n=30)		Group 2 (n=30)		P value
	No.	%	No.	%	
No ADRs	27	90%	25	83.33%	0.44
Bradycardia	1	3.33%	0	0 %	0.31
Bradycardia+ Hypotension	1	3.33%	0	0 %	0.31
Tachycardia	0	0%	2	6.66%	0.14
Tachycardia+ Hypertension	1	3.33%	3	10%	0.29

DISCUSSION

Etomidate [R-1-(1-ethylphenyl) imidazole-5-ethyl ester] is a unique drug used for induction of general anaesthesia and sedation. Among induction drugs, etomidate is the only imidazole, and it has the most favourable therapeutic index for single bolus administration. With a stable cardiovascular profile and minimal respiratory side effects, etomidate is widely used for general induction with clinical features such as a fast onset of action and short half-life.

Etomidate exerts its effect on GABA receptors by binding directly to a specific site or sites on the protein and enhancing the affinity of the inhibitory neurotransmitter (GABA) for these receptors. It has two common adverse effect, pain on injection and myoclonus. Myoclonus is defined as sudden, brief, involuntary muscle jerks either irregular or rhythmic, and has been reported in 50 – 80% of patients receiving etomidate. However, the exact mechanism of etomidate induced myoclonus remains unclear. Following reasons have been proposed. First, spontaneous nerve transmissions may occur when pathways associated with skeletal muscle control become more sensitive with the interruption of GABA neurons. Second, several studies have demonstrated that etomidate induced myoclonus might be associated with a seizure-like activity. Third, the inhibitory circuits are depressed earlier than excitatory neuronal circuits after injection of Etomidate.

In the present study, we have compared the effect of dexmedetomidine and fentanyl as a premedication for prevention of etomidate induced myoclonus. Dexmedetomidine is a highly selective α2 agonist. It has potent sympatholytic, analgesic and sedative properties mediated through α2-adrenoceptors in the central and peripheral nervous system without significant respiratory depression. α2 adrenergic receptors are commonly found in synapses, postsynaptic parts of the central nervous system, peripheral nerves and autonomic ganglia. Stimulating synaptic α2 receptors in sympathetic nerve endings can inhibit the release of norepinephrine. Before anaesthesia, intravenous injection of the drug can significantly reduce the stress responses of laryngoscope and endotracheal intubation. Therefore, the effect of dexmedetomidine in relieving myoclonus may be related to its sedative and analgesic effects.

Mizrak et al.[3] observed that pretreatment with dexmedetomidine (0.5 mcg /kg) or thiopentone (1 mg/kg) were useful in reducing the incidence and intensity of myoclonic movements during induction of anaesthesia with etomidate. They observed that, the incidence of myoclonus was 34% in group dexmedetomidine, 37% in group thiopentone, and 64% in group C (control 63 group). The incidence of severe myoclonic movements (grade 3) was 30% in group C, 13% in group dexmedetomidine and 13% in group thiopentone.

In our study, mean age of patients in Group 1 was 34.27 years and in Group 2 was 34.30 years, while in the study by Shui Miao et al.,[4]Mean age in one of the groups was 47.6 years and in other group was 49.8 years. Mean weight in Group 1 was 63.4 Kg and in Group 2 was 67.57 Kg in our study, while in study by Shui Miao et al.,[4] mean weight was 72.2 Kg in one group and 71.2 Kg in other group.

Shui Miao et al.[4] had observed that pretreatment with dexmedetomidine 0.5 mcg /kg resulted in a 38% reduction in the number of patients who experienced myoclonus in comparison to patients who received only Normal saline. Based on results of this study, we chose the 0.5 mcg /kg dose of dexmedetomidine for our study.

Opioids reduce the frequency of myoclonic movements, however the mechanism by which this effect is achieved remains unclear. Fentanyl is a μ- receptor agonist that causes dose-dependent analgesia, respiratory depression and sedation. Honar et al. concluded that the anti-seizure effect of opioids is thought to be mediated through inhibitory effects on excitatory pathways and increasing GABAergic tone. These are probably the reasons why opioids reduce the myoclonic movement.

Stockham et al.[13] reported that premedication with fentanyl decreased etomidate-induced myoclonus in a dose-dependent manner, but it increased the risk of apnea. They observed that none of the patients who received premedication with 500 mcg fentanyl 5 minutes before anesthesia induction using etomidate had a myoclonus, but all developed apnea. Respiratory depression was less when 100 mcg fentanyl was given, and the rate of myoclonus was 33%. Based on the results of this study, we chose the 1 mcg /kg dose of inj. fentanyl for our study.

There is no study evaluating the comparison of effect of dexmedetomidine and fentanyl as a premedication on the incidence of etomidate induced myoclonus. That's why this study was

conducted to compare the effect of inj. dexmedetomidine 0.5 mcg /kg (Group 1) and inj. Fentanyl 1 mcg /kg (Group 2) for prevention of Etomidate induced myoclonus.

In our study, we observed that 63.33% patients in Group 1 and 50% patients in Group 2 did not suffer from myoclonus after administration of study drug, which was statistically significant. So, dexmedetomidine was more effective in prevention of etomidate induced myoclonus as compared to fentanyl. Among patients who developed myoclonus, we observed that 26.66%, 10% and 0% patients in Group 1 & 33.33%, 13.33% and 3.33% patients in Group 2 had myoclonus of grade 1,2 and 3, respectively. However, the difference in severity reduction between two groups was not significant. There was no statistically significant difference between 2 groups in demographic data like age and sex. There were no major intra operative side effects except 1 patient had bradycardia, 1 had hypotension with bradycardia and 1 had hypertension with tachycardia in Group 1 & 2 had tachycardia and 3 had hypertension with tachycardia in group 2, which was statistically not significant.

Our study had few limitations. First, we did not take placebo group in our study to compare because the incidence of myoclonus in non-premedicated patients is as high as 80%. Also, we have taken safe minimal dose of the dexmedetomidine and fentanyl to prevent side effects such as bradycardia and respiratory depression.

CONCLUSION

From this study, we concluded that incidence of etomidate induce myoclonus was significantly decreased in patients with pretreated with inj. dexmedetomidine 0.5 mcg /kg as compared to inj. fentanyl 1 mcg /kg. But in terms of severity grading, difference between these two drugs was insignificant. Both the drugs provide stable hemodynamic during general anaesthesia.

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