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"A PROSPECTIVE COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MIDAZOLAM FOR PREVENTION OF ETOMIDATE INDUCED MYOCLONUS AND ATTENUATION OF STRESS RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION"

Anaesthesiology

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ABSTRACT

Background & Aims: Myoclonus is the most common side effect of etomidate used as induction agent for general anaesthesia. A lot of drugs have been tried so far to minimize the occurrence as well as intensity of myoclonus following etomidate injection. In this study we compared the effect of dexmedetomidine & midazolam for prevention of myoclonus, attenuation of stress reponse to laryngoscopy and endotracheal intubation. **Method:** This study was prospective, comparative, randomized interventional study conducted in department of Anaesthesiology, in Major Surgical operation theaters in civil hospital, Ahmedabad, within a duration of 8 months from April 2022-November 2022, which was conducted on ninety patients with age more than 14 yrs and ASA grade I, II, III undergoing elective surgery under general anaesthesia, were randomly allocated into three groups of 30 patients each. Intravenous injection of etomidate 0.3mg/kg given, myoclonus was observed and graded, after 2 min inj succinylcholine was given to facilitate intubation. Intraop hemodynamic parameters observed at various time intervals, statistical analysis done using epi info software. P value less than 0.05 was considered as significant. **Result:** Myoclonus was observed in 66.6% of Group C after administration of inj etomidate, while it was observed in 30% patients of Group 1(DEX) and 50% patients of Group 2(MIDAZ). Hence the incidence of etomidate induced myoclonus was least in Group 1(DEX) and less in Group 2(MIDAZ) compared to Group C. Reduced stress response to laryngoscopy & intubation were observed in Group 1(DEX) & Group 2 (MIDAZ) than control group. Intraoperative hemodynamic stability was comparable in Group 1(DEX) & Group 2 (MIDAZ) than control group. **Conclusion:** We conclude that incidence of etomidate induced myoclonus was significantly decreased among patients who underwent pretreatment with dexmedetomidine in comparision with patients who underwent pretreatment with midazolam. Whereas the incidence was increased significantly when etomidate was used alone. Reduced stress response to laryngoscopy & intubation were observed in patients who underwent pretreatment with midazolam & dexmedetomidine than control group.

KEYWORDS

Etomidate, Midazolam, Dexmedetomidine, Myoclonus

INTRODUCTION

Etomidate directly works on gamma aminobutyric acid (GABA) receptors. It is sedative hypnotic agent which is derived from the imidazole group. It blocks neuroexcitation to produce anaesthesia and it is known to have insignificant effects on respiratory system along with relatively stable hemodynamic profile in comparison with other induction agents. Most common side effects of etomidate include pain at the site of injection and myoclonus. Incidence of pain was reduced with the newer fat emulsion preparations but no decrease in the incidence of myoclonus was seen.[1,2]. Myoclonus occurs in almost 80% of the patients, who were not medicated after the induction of anaesthesia with the injection etomidate. A lot of drugs have been tried so far to minimize the occurrence as well as intensity of myoclonus following the etomidate injection, which include opioids, midazolam, magnesium sulphate and rocuronium[8-10]. Among many new agents being used for premedication to reduce myoclonus is dexmedetomidine. In current study, we compared the effectiveness of midazolam with that of dexmedetomidine in decreasing the occurrence as well as severity of myoclonus among the patients who were anaesthetized with etomidate, as a primary objective. Moreover, we compared the efficacy of both agents in decreasing the stress response to laryngoscopy, intubation & intraoperative hemodynamic parameter.

MATERIAL AND METHOD

Study Design

- Study type: prospective, comparative, randomized interventional study
- Study site: Department of Anaesthesiology in Major Surgical operation theaters in Civil Hospital, Ahmedabad
- Study duration: 8 months from April 2022- November2022
- Study size: conducted on ninety patients undergoing elective surgery after informed and written consent.

Drugs

The study involved use of etomidate as induction agent in general anaesthesia and sevoflurane as inhalational anaesthetic agent, O2 and atracurium besylate as muscle relaxant for maintenance; also dexmedetomidine and midazolam used as study drugs for prevention of myoclonus. Drugs were in Government supply at CHA.

Patient Criteria:

Inclusion Criteria:

- Consent
- Age>14yrs
- ASA grading I,II,III

Exclusion criteria:

- Refusal to give consent
- Age <14 years
- ASA grade IV-V
- Known allergies to anaesthetic drugs and study.
- Patients hemodynamically or neurologically unstable.
- Patient having neurological or psychiatric disorder.

Following the approval by Institutional ethical committee, after obtaining written, informed consent from patients & patient's relatives, study was done. Ninety patients, aged>14years, ASA grade I-II-III, scheduled to undergo general anaesthesia were included in the study. Preoperative assessment was done and investigations were noted. In operation theatre intravenous cannula of proper size was inserted into the largest vein on the forearm and an infusion of DNS was started at

the rate of 5 ml/kg/hr. All the patients were pre-medicated with intravenous glycopyrrolate 0.004mg/kg, ondansetron 0.15mg/kg and Inj. fentanyl 1mcg/kg. ECG, NIBP, SpO2 were monitored. Baseline hemodynamic parameters were recorded. All the patients were preoxygenated with 100% O2 for 3mins.Patients were randomly divided to one of the following three groups of 30 patients each as per study drug injected. Group1(DEX): Patient received loading dose Dexmedetomidine of 0.5mcg/kg in 100ml NS as Pre medication & Etomidate(0.3mg/kg) as induction agent.Group2(MIDAZ)**:** Patient received loading dose Midazolam of 0.015mg/kg in 100ml NS as premedication & Etomidate(0.3mg/kg) as induction agent. Group C (CONTROL): Historical control group based on previous study taken of patients who received Etomidate(0.3mg/kg) as induction agent. 60 sec after injection of etomidate myoclonus was observed and recorded in severity grades as follows

0 = no myoclonus
1 = mild myoclonus (small movements in I body segment, such as finger or wrist)
2 = Moderate myoclonus (slight movements in 2 or more muscle areas, such as face or shoulder)
3 = Severe (intense movement in 2 or more muscle area, sudden adduction of an extremity)

Inj. Succinylcholine 2mg/kg IV given 2 min after etomidate injection to facilitate intubation. Patient was intubated with appropriate sized endotracheal tube. After checking bilateral air entry, cuff inflated and tube fixed. Maintenance: 100% O2 mixture with Sevoflurane traces 1.5–2% and Inj. Atracurium Besylate. All patients were mechanically ventilated with tidal volume of 6ml/kg body weight and frequency of 12 cycles per minute using ventilator.After the completion of surgery, neuromuscular blockade was reversed with Inj.Glycopyrrolate 8µg/kg and Inj.Neostigmine 50µg/kg. After thorough Oral and Endo- tracheal suction, extubation was done.

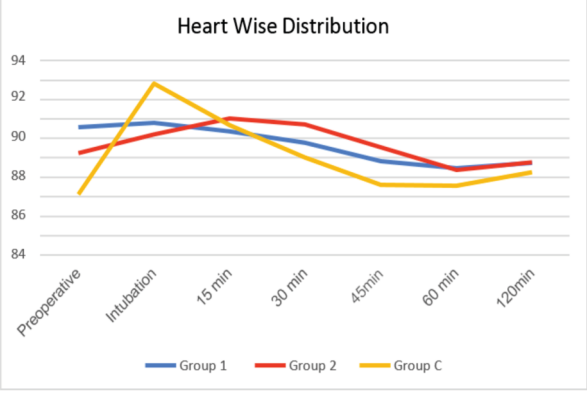
Statistical Analysis:
Data was entered in Microsoft excel and analysed using Epi-Info software. Continuous variables was expressed as mean standard deviation. Appropriate statistical tests was applied accordingly. Logistic regression was done for multivariate analysis. P-value less than 0.05 was considered as significant.

Study End Point: Till December 2022

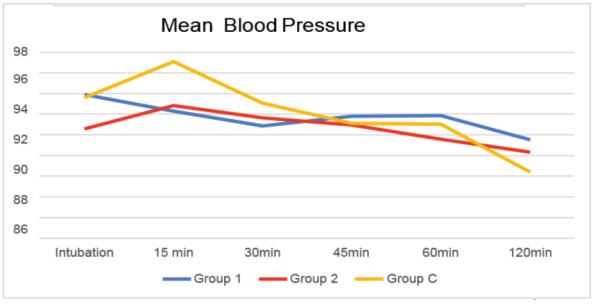
RESULTS

This study included 90 patients. The patients were randomly assigned in to 3 groups including 30 patients in each group by randomized computer sampling technique. We included Group 1 (Dexme detomidine), Group 2 (Midazolam) and Group C (control) in study. Historical control group based on previous study taken of patients who received etomidate as induction agent. ANOVA test and Chi square test were used for statistical analysis. Data was entered in Microsoft excel and analysed using Epi-Info software. If p value is <0.05, statistically not significant If p value is > 0.05 statistically significant.

- Demographic parameters like age, weight, and gender were comparable in all the 3 study groups. p value of three groups is 0.5 which is not statistically significant.
- Heart rate increases in Group C during and after intubation compared to Group 1(DEX) and Group2 (MIDAZ). However the difference in heart rate among these three groups were not statistically significant (p>0.05)



- SBP increases in Group C during and after intubation compared to Group 1(DEX) and Group2 (MIDAZ). However the difference in SBP among these three groups were not statistically significant (p>0.05)
- DBP increases in Group C during and after intubation compared to Group 1(DEX) and Group 2 (MIDAZ). However the difference in DBP among these three groups is not statistically significant (p>0.05).
- MAP increases in Group C during and after intubation compared to Group 1(DEX) and Group 2 (MIDAZ). However the difference in MAP among these three groups is not statistically significant (p>0.05)



- Myoclonus was observed in 66.66% patients of group C after administration of inj. etomidate, while it was observed in 30% patients of Group1 (DEX) and 50% of patients of Group 2 (MIDAZ). Thus it was observed that occurrence of myoclonus was less in Group 1(DEX) as compared to Group 2 (MIDAZ) and Group C which is statistically significant as p value is < 0.05

Table 1: Myoclonus grading

Myoclonus Grading	Group 1 (n=30)	Group 2 (n=30)	Group C (n=30)	P value
Grade 0	21(70%)	15(30%)	10(33.33%)	0.0178
Grade 1	7(23.33%)	6(22.22%)	2(6.66%)	0.1863
Grade 2	2(6.66%)	7(22.33%)	10(33.33%)	0.0380
Grade 3	0(0%)	2(6.66%)	8(22.6%)	0.0116

DISCUSSION

In this study we compared dexmedetomidine and midazolam for prevention of etomidate induced myoclonus and attenuation of stress response to laryngoscopy and endotracheal intubation. Even though etomidate is considered to be a safe induction agent with low risk of hypotension, it has two common adverse effect, pain on injection and myoclonus. Pain on injection is minimised by new fat emulsion of etomidate but myoclonus (myoclonus is defined as sudden, brief, involuntary muscle jerks either irregular or rhythmic) is still a clinical problem[11,12].

However, the exact mechanism of etomidate induced myoclonus remains unclear. It may be explained by the following reasons for the occurrence of myoclonus. First, spontaneous nerve transmissions may occur when pathways associated with skeletal muscle control become more sensitive with the interruption of GABA neurons[13]. Second, several studies have demonstrated that the etomidate induced myoclonus might be associated with a seizure-like activity[14]. Third, the inhibitory circuits are depressed earlier than excitatory neuronal circuits after injection of Etomidate[15].

Dexmedetomidine is a highly selective α2 agonist. Dexmedetomidine has potent sympatholytic, analgesic and sedative properties mediated through α2- adrenoceptors in the central and peripheral nervous system without significant respiratory depression. 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[16]. Midazolam is a water soluble benzodiazepine which act on GABA which is inhibitory neurotransmitter in CNS Midazolam causes anterograde amnesia, used as a sedative and relatively mainatain stable hemodynamics.

In our study in Group C heart rate was increased during intubation compared to Group 1 (DEX) Group 2 (MIDAZ), but p value was > 0.05, hence not significant. The baseline, premedication, during induction and intraop value of systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were comparable in three

groups. In Group C there were slightly increased SBP, DBP and MAP values during intubation and were found to be regularized after 10-15 mins. In Group 1(DEX) and Group 2(MIDAZ) it was found that there was less variation in SBP, DBP, MAP compared to Group C but p value at various time intervals remained insignificant (p>0.05).

Gupta P et al[17] [2022] have concluded that based on the observations of their study, pretreatment with 0.5µg/kg and 1µg/kg dexmedetomidine significantly reduce etomidate induced myoclonus and stress response at intubation. However, dexmedetomidine in dose of 0.5µg/kg is associated with fewer side effects of bradycardia and hypotension.
In our study bradycardia and hypotension were not observed.

Shui Miao, et al. has observed that pretreatment with dexmedetomidine 0.5mcg/kg resulted in a 38% reduction in the number of patients who experienced myoclonus in compare to patients who received only Normal saline.[10]

We have analyzed that 30% of patients of Group 1(Dex), 50% of patients in Group 2(Midaz) and 66.6% in Group C had incidence of myoclonus. There is visible difference between 3 groups. This difference is statistically significant as p value is <0.05.

We concluded that pretreatment with 0.5µg/kg and 1µg/kg dexmedetomidine significantly reduce etomidate induced myoclonus and stress response at intubation. However, dexmedetomidine in dose of 0.5µg/kg is associated with fewer side effects of bradycardia and hypotension. In our study bradycardia and hypotension were not observed.

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. We have analyzed that 30% of patients of Group 1(Dex), 50% of patients in Group 2(Midaz) and 66.6% in Group C had incidence of myoclonus. There was visible difference between 3 groups. This difference is statistically significant as p value is <0.05. Strength of our study is we compared premedication with dexmedetomidine and midazolam injection to reduced etomidate induced myoclonus, stress response to laryngoscopy and intubation with control group. Study design had some limitation, we did not measure plasma cortisol and adrenocorticotropic hormone level due to non-availability of the above test in our institution and we did not include high risk patients.

CONCLUSION

We conclude that incidence of etomidate induced myoclonus was significantly decreased among patients who underwent pretreatment with dexmedetomidine in comparison with patients who underwent pretreatment with midazolam. Whereas the incidence was increased significantly when etomidate was used alone. Reduced stress response to laryngoscopy & intubation were observed in patients who underwent pretreatment with midazolam & dexmedetomidine than control group .Intraoperative hemodynamic stability was comparable in patients who underwent pretreatment with midazolam & dexmedetomidine than control group

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