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Comparative study between dexmedetomidine and midazolam as pre-medication for the prevention of etomidate-induced myoclonus and attenuation of stress response at endotracheal intubation in laparoscopic cholecystectomies

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ABSTRACT

Background: Myoclonus is a common issue in etomidate anesthesia induction, and various drugs have been used to reduce its incidence, highlighting the ongoing search for better alternatives in anesthesiology. **Aims and Objectives:** The study analyzed the impact of dexmedetomidine (DEX) and midazolam pre-treatment on etomidate-induced myoclonus incidence, stress response at laryngoscopy, and intubation during etomidate induction. **Materials and Methods:** A prospective randomized controlled intervention study (superiority trial) was done involving 42 patients of age 20–60 years, randomly allocated in two equal groups (Group D: Inj. DEX was given as infusion (0.5 µg/kg) in 10 mL 0.9% normal saline over 10 min and 5 min before induction. Group M: Inj. Midazolam was given 0.02 mg/kg, prepared in 10 mL 0.9% normal saline, to be infused over 10 min and 5 min before induction). Myoclonus was graded after intravenous administration of etomidate (0.3 mg/kg) and hemodynamic response to laryngoscopy and intubation were observed at various time intervals. Statistical analysis was done using SPSS version 27.0. Independent t-test/Mann–Whitney test (for non-parametric data) and Chi-square test/Fisher's exact test were used to compare variables. A $P<0.05$ was considered statistically significant. **Results:** The study found that DEX effectively suppressed stress response due to intubation compared to midazolam, with mean myoclonus gradation (Mean ± SD) in Group-D and Group-M being 0.6190 ± 0.7400 and 1.6667 ± 0.8563, respectively, indicating a significant distribution with group. **Conclusion:** DEX was found to be more effective than midazolam in preventing etomidate-induced myoclonus and attenuating stress response compared to midazolam.

Key words: Dexmedetomidine; Midazolam; Etomidate; Myoclonus; Laparoscopic cholecystectomy

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INTRODUCTION

Today, the most effective surgical procedure for treating cholelithiasis is laparoscopic cholecystectomy.[1] An increase in plasma renin activity, an increase in plasma catecholamine levels, and an increase in the volume of blood in circulation due to blood moving from the splanchnic capacitance vessels to the systemic circulation are all immediately followed by pneumoperitoneum, which also raises intra-abdominal pressure.[1] Despite many

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benefits, all laparoscopic surgeries are challenging from an anesthetist's perspective, mainly due to significant alteration of hemodynamics.[2]

All elective laparoscopic cholecystectomy surgeries are performed under general anesthesia.

To maintain artificial positive pressure ventilation and secure the airway during a surgical procedure, endotracheal intubation through direct laryngoscopy is a necessary pre-condition for general anesthesia. After the patient has fully recovered from the effects of the anesthetic and muscle relaxants and has regained protective airway and other reflexes, endotracheal extubation is performed at the conclusion of the procedure.

There are several types of hemodynamic abnormalities that can occur during intubation under direct laryngoscopy, including tachycardia (or bradycardia) and hypertension with or without arrhythmia.[3,4] Normal people can handle this reaction, but in vulnerable people, this brief sympathetic reaction might result in potentially fatal situations.[5]

Dexmedetomidine (DEX) is a potent, selective α-2 agonist with a 2-h elimination half-life and is seven to ten times more selective than clonidine. It has a shorter action duration and is considered a full agonist at α-2 receptors. Similar to clonidine, it attenuates the hemodynamic response to tracheal intubation and decreases plasma catecholamine concentration during anesthesia.[6]

Etomidate is a sedative-hypnotic agent that acts on the gamma-aminobutyric acid receptor complex, blocking neuroexcitation and producing anesthesia. It has a stable hemodynamic profile and minimal respiratory system effects. Common side effects include pain on injection and myoclonus.[7] Although a new fat emulsion preparation has eliminated these side effects, the new solvent has not reduced myoclonus incidence.

Myoclonus is a common problem during the induction of anesthesia with etomidate.

Midazolam is a benzodiazepine group of drug, which is an anxiolytic, sedative, hypnotic, and amnestic drug and has been widely used as pre-medication. It is effective in reducing separation and induction anxiety.

The present study had been designed to ascertain an ideal pre-treatment drug which can abolish or significantly reduce the incidence of etomidate-induced myoclonus and also cause attenuation of stress response of laryngoscopy and intubation. The primary aim of our study was to compare the incidence and severity of myoclonus in both study groups. The secondary objective was to compare the attenuation of hemodynamic changes of laryngoscopy and intubation in both groups.

Aims and objectives

Aim

The aim of the study is to conduct a comparative evaluation of pre-treatment with DEX with midazolam for the prevention of etomidate-induced myoclonus and attenuation of stress response at intubation in laparoscopic cholecystectomy.

Objectives

a. To compare the myoclonus gradation in both groups
b. To measure and compare heart rate (HR) in both groups
c. To measure and compare mean arterial pressure (MAP) in both groups
d. Incidence of adverse effects if any.

MATERIALS AND METHODS

This is a prospective randomized controlled intervention study (superiority trial) and was conducted in the Department of Anaesthesiology in Bankura Sammilani Medical College, Bankura, after permission of the Institutional Ethical Committee. Patients undergoing elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation at general surgery operation rooms were selected as study population. The present study was registered in CTRI: CTRI/2022/09/045476.

Patients were selected after thorough pre-anesthetic assessment and investigations. 42 patients were divided into two groups, Group D and Group M with 21 cases in each group by matching patient's age, sex, Mallampati score, and ASA grading (I or II). Patient's allocation in the arms was done using method of randomization by minimization.

Group D: DEX group – here, DEX was given as infusion (0.5 μg/kg) in 10 mL 0.9% normal saline over 10 min and 5 min before induction.

Group M: Midazolam group – here, midazolam was given at dose 0.02 mg/kg, prepared in 10 mL 0.9% normal saline, to be infused over 10 min and 5 min before induction.

Inclusion criteria

The patients between 20 and 60 years belonging to ASA grade I and II and those were scheduled for elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation were selected.

Exclusion criteria

Those unwilling, morbidly obese patients, of ASA class III, IV, and V with difficulty in intubation, who had allergies to study drugs, labile blood pressure, severe renal, endocrine, cardiac dysfunction, heart block, those with alcohol/drug abuse history, and pregnant and lactating patients were excluded from the study.

Age, sex, weight and height of patient, HR, MAP, and myoclonus gradation were study variables.

Written informed consent was taken from the willing participants after proper explanation of study procedure and expected outcome in their own vernacular language.

Randomization

Patients were randomly allocated into 2 groups using a computer-generated random number list.

Pre-operative assessment

On the day before surgery, each patient was attended and examined properly for a pre-operative counseling and repeat anesthetic check-up. Pre-anesthetic evaluation was performed in each patient including detailed history taking, thorough physical examination, and relevant pre-operative investigations. The nature and procedure of the study were explained to the patients. All patients were undergo pre-operative fasting for 6–8 h before surgery.

Patient's Preparation – the day before surgery, Tab. Alprazolam (0.25 mg) at bedtime and on the day of surgery, Tab. Pantoprazole (40 mg) and Tab. Domperidone (10 mg) were given. On arrival in the operation room, ASA standard monitors were attached. SpO_2, ECG, and HR were monitored continuously and non-invasive recordings of systolic, diastolic, and MAP were taken. An IV line was started with Ringer's lactate solution after putting an 18G cannula.

Procedure

Patients in Group D and Group M were given injection DEX infusion (0.5 μg/kg) and injection midazolam (0.02 mg/kg), respectively, in 10 mL normal saline over 10 min. The patient was pre-oxygenated with 100% oxygen for 3 min before induction with a tight-fitting facemask. Anesthesia was induced with Inj. Etomidate (0.3 mg/kg) over 30 s or till the abolition of eyelash reflex was observed and intubation was facilitated with injection Atracurium 0.5 mg/kg intravenously. Laryngoscopy was done using rigid laryngoscope with standard Macintosh blade. Intubation was done with an appropriate-sized disposable, high-volume low pressure-cuffed endotracheal tube. After confirming the position of the tube, the patient was ventilated with gas mixture of 33% oxygen and 66% nitrous oxide with a tidal volume of 8–10 mL/kg and a rate of 12–15 breaths/min to maintain end-tidal CO_2 in the range of 35–40 mmHg. Maintenance of anesthesia was done using relaxant Inj. Atracurium maintenance dose (0.1 mg/kg) as and when required along with inhalational agent Isoflurane (0.5–1%). Patient's pulse rate, non-invasive blood pressure (systolic, diastolic, MAP), electrocardiogram, and SpO_2 were monitored. After the injection of the study drug and etomidate, the presence of myoclonus was recorded in all patients and if present, the severity was graded by a person blinded to the treatment group.

HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and SpO_2 were measured before giving study drug (S0); after giving study drug (S1); before induction (T0); 1 min after intubation (T1); 3 min after intubation (T3); 5 min after intubation (T5). Throughout the procedure, any change in the MAP of over 20% of the basal value was countered by increments of intravenous Inj. Mephentermine 3 mg. HR <50 beats/min was treated by administering Injection Atropine 0.6 mg. At the end of operation, residual neuromuscular block was reversed by giving neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). When patient's respiration became spontaneous and regular and they were able to obey simple commands, and suctioning and extubation were done. Before discharging the patient from post-operative recovery room, any adverse effect such as sedation, hypotension, bradycardia, nausea, vomiting, and dryness of mouth, if observed, was recorded. All the observations were recorded in the attached pro forma for subsequent statistical analysis.

Relevant investigations were included complete blood count, serum urea, serum creatinine, serum glucose random, liver function test with enzymes.

Statistical analysis was done using SPSS version (version 27.0; SPSS Inc., Chicago, IL, USA). Independent t-test/Mann–Whitney test (for non-parametric data) and Chi-square test/Fisher's exact test were used for statistical analysis. A $P<0.05$ was considered statistically significant.

RESULTS

Distribution of mean age and weight in Kg within groups was not statistically significant (Table 1). Distribution of sex within groups was not statistically significant (P=1.0000).

Table 1: Comparison of demographic characteristics between groups

Age and weight	Group-D	Group-M	P-value
Age	39.7619±9.7566	39.4762±9.4743	0.9238
Weight (kg)	63.4762±8.5242	64.2857±9.1932	0.7688

Distribution of mean HR with groups was not statistically significant except mean HR-T1 which was statistically significant (P=0.0008) (Table 2).

Distribution of mean MAP with groups was not statistically significant except mean MAP-T1 which was statistically significant (P=0.0043) (Table 3).

Distribution of mean myoclonus gradation with group was statistically significant (P=0.0001) (Table 4 and Figure 1).

Two groups were comparable regarding adverse effects (nausea and vomiting).

DISCUSSION

The present study was a prospective randomized controlled intervention study. Total 42 patients were included in this study after proper pre-anesthetic assessment and investigation and were divided into two groups, Group D and Group M with 21 patients in each group by

Table 2: Distribution of mean HR at different time intervals: Group

Heart Rate	Number	Mean	SD	Minimum	Maximum	Median	P-value
HR-S0							
Group-D	21	80.7619	7.9492	66.0000	92.0000	80.0000	0.8812
Group-M	21	80.3810	8.4586	66.0000	94.0000	82.0000	
HR-S1							
Group-D	21	79.2381	6.5947	67.0000	90.0000	80.0000	0.7534
Group-M	21	78.5714	7.0539	68.0000	90.0000	80.0000	
HR-T0							
Group-D	21	79.5238	6.8820	68.0000	92.0000	81.0000	0.8209
Group-M	21	79.0476	6.6594	69.0000	92.0000	80.0000	
HR-T1							
Group-D	21	86.4286	5.7756	76.0000	98.0000	86.0000	0.0008
Group-M	21	94.0000	7.5829	79.0000	110.0000	96.0000	
HR-T3							
Group-D	21	84.4762	4.6002	76.0000	94.0000	84.0000	0.0636
Group-M	21	87.4762	5.5463	78.0000	100.0000	89.0000	
HR-T5							
Group-D	21	81.7619	3.9863	75.0000	90.0000	82.0000	0.9018
Group-M	21	81.5714	5.7929	68.0000	89.0000	84.0000	

HR: Heart rate

Table 3: Distribution of mean MAP at different times interval: Group

MAP	Number	Mean	SD	Minimum	Maximum	Median	P-value
MAP-S0							
Group-D	21	97.9524	4.6741	89.0000	108.0000	99.0000	0.7618
Group-M	21	98.4286	5.4090	87.0000	108.0000	99.0000	
MAP-S1							
Group-D	21	96.5238	4.7814	87.0000	107.0000	97.0000	0.8982
Group-M	21	96.7143	4.8077	89.0000	107.0000	97.0000	
MAP-T0							
Group-D	21	96.1905	4.5893	87.0000	104.0000	97.0000	0.8365
Group-M	21	95.9048	4.3232	88.0000	105.0000	97.0000	
MAP-T1							
Group-D	21	101.9524	3.5704	95.0000	111.0000	101.0000	0.0043
Group-M	21	105.8095	4.6219	98.0000	114.0000	105.0000	
MAP-T3							
Group-D	21	99.3333	3.6515	93.0000	105.0000	99.0000	0.1286
Group-M	21	101.1429	3.9024	95.0000	110.0000	100.0000	
MAP-T5							
Group-D	21	94.3333	3.8123	87.0000	101.0000	95.0000	0.8723
Group-M	21	94.5238	3.8160	87.0000	101.0000	95.0000	

MAP: Mean arterial pressure

Table 4: Distribution of mean myoclonus gradation: Group

Myoclonus	Gradation	Number	Mean	SD	Minimum	Maximum	Median	P-value
Myoclonus	Group-D	21	0.6190	0.7400	0.0000	2.0000	0.0000	0.000
Gradation	Group-M	21	1.6667	0.8563	0.0000	3.0000	2.0000	1

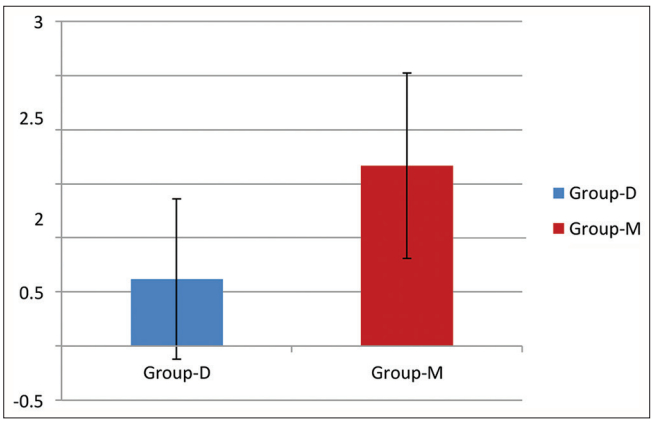

Figure 1: Distribution of mean myoclonus gradation: Group

matching patient's age, sex, Mallampati score, and ASA grade (I and II).

Vijayan et al.,[8] in their study, they evaluated the efficacy of pre-medication with DEX, pregabalin, and DEX-pregabalin combination for attenuating the hemodynamic stress response to laryngoscopy and intubation and pneumoperitoneum (primary outcome) and for reducing anesthetic requirement (secondary outcome) in patients undergoing laparoscopic cholecystectomy.

In their study, it was found that, mean age and mean body weight (kg) were not statistically significant in both group Group-D and Group-M, which was similar to our study.

Moreover, in our study, HR-S0 (P=0.8812), HR-S1 (P=0.7534), HR-T0 (P=0.8209), HR-T3 (P=0.0636), and HR-T5 (P=0.9018) were not statistically significant in both group Group-D and Group-M and HR-T1 (P=0.0008) was statistically significant in both group Group-D and Group-M, and these results are similar to study done by Vijayan et al.[8]

Sulaiman et al.,[9] examined that this study was designed to study the efficacy of intravenous DEX for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation in patients with coronary artery disease.

This study showed that the DEX group had a better control of hemodynamics during laryngoscopy and endotracheal intubation which is similar to our study.

Jain et al.,[10] took sixty patients of ASA I and II and were randomly divided into two groups. Group D patients received an injection of DEX at a dose of 1 μg/kg, whereas group F patients received an injection of fentanyl at a dose of 2 μg/kg preoperatively over 10 min before induction of anesthesia with an injection of thiopentone and vecuronium.

This study showed that DEX significantly attenuated the sympathetic response to laryngoscopy and intubation in terms of HR, SBP, and DBP compared with fentanyl which is similar to our study where we used midazolam instead fentanyl.

Chandra and Mukherjee[11] examined that laryngoscopy and intubation were painful stimuli which invoked responses such as tachycardia, hypertension, and arrhythmias.

We observed that MAP-S0 (P=0.7618), MAP-S1 (P=0.8982), MAP-T0 (P=0.8365), MAP-T3 (P=0.1286), and MAP-T5 (P=0.8723) were not statistically significant in both group Group-D and Group-M but MAP-T1 (P=0.0043) was statistically significant in both group Group-D and Group-M which is similar to study done by Chandra and Mukherjee.[11]

Luan et al.,[12] observed that myoclonus induced by etomidate during induction of general anesthesia was undesirable. This study evaluated the effect of DEX pre-treatment on the incidence and severity of etomidate-induced myoclonus. In this study, pre-treatment with 0.5 and 1.0 μg/kg DEX significantly reduced the incidence of etomidate-induced myoclonus during anesthetic induction; however, 0.5 μg/kg DEX was recommended because it had fewer side effects. This result is similar with our study.

Du et al.,[13] investigated the effect of DEX in the prevention of etomidate-induced myoclonus.

In our study, the incidence of etomidate-induced myoclonus in the DEX-treated groups was significantly lower than that of midazolam group. This result correlates with study done by Du et al.[13]

In our study, there is statistically significant difference between etomidate-induced myoclonus in the DEX-treated groups and that of the midazolam-treated groups. Thus, our study differs from above study.

Dey and Kumar et al.,[14] showed that myoclonus is a common problem during induction of anesthesia with etomidate. A variety of drugs have been used to decrease the incidence of myoclonus. In this study, they compared the effects of DEX and midazolam pre-treatment on the incidence of etomidate-induced myoclonus. They also studied the effects of these drugs on attenuation of stress response at laryngoscopy and intubation on induction with etomidate.

In our study, the mean myoclonus gradation was higher (1.6667±0.8563) in Group-M compared to Group-D (0.6190±0.7400) and it was statistically significant (P=0.0001). Stress response due to intubation was more effectively suppressed by DEX as compared to midazolam.

Therefore, the result of our study is in concordance with the other studies.

Limitations of the study

In spite of every sincere effort, my study has lacunae.

The notable shortcomings of this study are:

1. The sample size was small. Only 42 cases are not sufficient for this kind of study
2. The study had been done in a single center
3. The study was carried out in a tertiary care hospital, so hospital bias cannot be ruled out
4. We evaluated only one dose of DEX and midazolam.

CONCLUSION

We came to the conclusion that DEX was a more effective pre-medication for preventing etomidate-induced myoclonus than midazolam. In addition, the DEX group showed a higher degree of stress response attenuation than the midazolam group did.

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SR- Manuscript preparation, editing, and manuscript revision; **MH-** Literature survey, data collection, data analysis; **SP-** Design of study, statistical analysis, and interpretation; **CB-** Definition of intellectual content, implementation of study protocol, review manuscript.

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