Original Article

Efficacy of Dexmedetomidine Versus Midazolam in Preventing Etomidate Induced Myoclonus and Reduction of Hemodynamic Stress Response Following Intubation, A Multicenter Trial

Liquat Ali[1], Muhammad Shahid[2], Malik Jamil Ahmed[3] and Aamir Furqan[4]

ABSTRACT

Objective: The effectiveness of dexmedetomidine versus midazolam in preventing etomidate induced myoclonus and reduction of hemodynamic stress response following intubation.

Study Design: A Randomized controlled trial.

Place and Duration of Study: This study was conducted at the Department of Anesthesia at Multan Medical and dental College, Bakhtawar Amin Hospital, Ch Pervaiz Ellahi Institute cardiology, Multan and Sahiwal Medical College Sahiwal from January 2018 to March 2019.

Materials and Methods: All 100 patients were indiscriminately allocated into two equal groups. Group-D was given dexmedetomidine and group-M was given midazolam. Age, weight, gender distribution, ASA status, hemodynamic factors (heart rate and mean blood pressure) and the incidence along with its severity were compared. Data was put in SPSS version 23 computer software and analyzed by applying Chi square and Independent t tests. P value ≤0.05 was considered of statistical importance.

Results: Age, weight, gender distribution and ASA status was not significantly different between Group D and Group M ($p > 0.05$). There was statistically noteworthy fall in post intubation heart rate as well as mean blood pressure in Group D as compared to Group M ($p<0.05$). Grade 0, 1, 2 and 3 myoclonus was seen in 56%, 30%, 16% and 2% patients of Group D; and 18%, 22%, 46% and 14% of the Group M patients, respectively ($p <0.001$).

Conclusion: In the patients who premedicated with dexmedetomidine, the incidence as well as the intensity of myoclonus was considerably lower as compared to patients who were premedicated with midazolam. Moreover, dexmedetomidine was a successful agent to significantly attenuate the hemodynamic stress responses of intubation.

Key Words: Dexmedetomidine, midazolam, hemodynamic stress response, myoclonus.

Citation of articles: Ali L, Shahid M, Ahmed MJ, Furqan A. Efficacy of Dexmedetomidine Versus Midazolam in Preventing Etomidate Induced Myoclonus and Reduction of Hemodynamic Stress Response Following Intubation, A Multicenter Trial. Med Forum 2019;30(6):73-77.

INTRODUCTION

Etomidate directly works on gamma aminobutyric acid (GABA) receptors. It is sedative hypnotic agent which is derived from the imidazole group.

[1.] Department of Anaesthesia, Multan Medical and Dental College, Multan.
[2.] Department of Anaesthesia, DHQ Teaching Hospital, Sahiwal.
[3.] Department of Anaesthesia, Bakhtawar Amin Medical and Dental College Multan.
[4.] Department of Anaesthesia, Ch. Pervaiz Ellahi Institute of Cardiology Multan.

Correspondence: Dr. Liquat Ali, Assistant Professor of Anaesthesia, Multan Medical and Dental College, Multan.
Contact No: 0300 8634525
Email: dr.liaqat.1953@gmail.com

Received: April, 2019
Accepted: May, 2019
Printed: June, 2019

It blocks neuroexcitation to produce anesthesia and it is known to have insignificant effects on respiratory system along with relatively stable hemodynamic profile in comparison with other anesthesia 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 anesthesia with the injection etomidate, increasing the vulnerability of regurgitation, aspiration as well as hypoventilation in non-fasting patients[3-6]. Myoclonus can be troublesome in cases of limited cardiovascular reserve and the patients with open eye injuries [3].

The jerky movements of myoclonus cases the detachment of the ECG leads in the patients on continuous monitoring which can lead to significant delay in monitoring and therefore, reduce the chances of successful timely intervention[6]. The neurologic

mechanism behind the occurrence of myoclonus following etomidate injection in not well understood yet. However, some researchers may suggest it to be some sort of seizure activity. In spite of the above effects, anesthesia induction with etomidate is smooth and provides favorable pharmacokinetics and toxicity profile which enables rapid recovery following single dose[7]. Etomidate can be used easily in the patients with shock, intracranial hypertension and respiratory diseases.

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[3], midazolam[8], magnesium sulphate [9] and rocuronium[10]. Among many new agents being used for premedication to reduce myoclonus is dexmedetomidine[11]. Dexmedetomidine has anxiolytic as well as analgesic activity. It acts on the alpha-2 adrenoceptors and is commonly used in intensive care and anesthesia [24]. It has recently been tried as premedication to decrease the occurrence as well as severity of myoclonus following etomidate induced anesthesia. The mode of action of dexmedetomidine in not yet clear.

Dexmedetomidine has been tried in various population but the data of its trial in Asian population is not available. In current study, we plan to match the effectiveness of midazolam with that of dexmedetomidine in decreasing the occurrence as well as severity of myoclonus among the patients who were anesthetized with etomidate, as a primary objective. Moreover, we plan to compare the efficacy of both the agents in lessening the hemodynamic stress responses of intubation.

MATERIALS AND METHODS

Our research is a prospective, randomized controlled trial which was directed Department of Anesthesia at Department of Anesthesia at Multan Medical and dental College, Bakhtawar Amin Hospital, Ch Pervaiz Ellahi Institute cardiology, Multan and Sahiwal Medical College Sahiwal, from January 2018 to March 2019. Sample size was calculated by taking the study by Dey S et al. [12] as reference. After taking the ethical approval from the Hospital Ethics Committee, 100 adult patients were selected. All the selected patients were to undergo surgical procedure under general anesthesia on elective basis. All the selected patients had American Society of Anesthesiologists (ASA) Grade I or II and gave informed consent for the study. All the patients who had previous history of any drug allergy, psychiatric disorders, systemic infections, sepsis, use of beta blocker drugs, and cardiac issues were not selected for the study.

All the participants were indiscriminately allocated into two equal groups. The patients in Group D were given dexmedetomidine (0.5 µg /kg) in the form of infusion in 10 ml of normal saline over a duration of 10 minutes, preceding the induction of general anesthesia. The patients in Group M were given midazolam (0.015 mg/ kg) in the form of infusion in 10 ml of normal saline over a duration of 10 minutes, preceding the induction of general anesthesia. Detailed pre anesthetic evaluation was done for all the patients. Alprazolam (0.25 mg) was provided to all the patients a night before and 2 hours preceding the surgery as pre medication in the form of tablet. Standard monitors were applied in the operation theatre. Intravenous cannulas were passed. Baseline heart rate along with mean arterial pressure was recorded. All the Group D patients received dexmedetomidine (0.5 µg/ kg) in the form of infusion in 10 ml of normal saline and the patients in Group M were given midazolam (0.015 mg/ kg) in the form of infusion in 10 ml of normal saline, over a duration of 10 minutes. Patients' ECG and SpO_2 were continuously monitored. Injection etomidate (0.3mg /kg) was given over 30 seconds or till eyelash reflex was diminished. Injection fentanyl 2µg /kg was given which was followed by injection vecuronium 0.1mg /kg for facilitating endotracheal intubation. Positive pressure ventilation was started with the help of bag and mask. N_2O and O_2 were given at 70:30 and 0.4 - 0.8% isoflurane were used as inhalational agents. Appropriate size cuffed endotracheal tube was passed. Heart rate along with mean blood pressure was documented prior to injection of study drug; after the injection of study drug and before intubation; and at 0, 1, 3 and 5 minutes following intubation. The presence of myoclonus was observed in all the patients after the administration of study drug and etomidate. Myoclonus was well-defined as the spontaneous contraction of a few fibers of one muscle or some muscles of a group which lead to noticeable movement of the matching body parts. In case of presence of myoclonus, the grade of myoclonus was also recorded. The scale used to classify the intensity of myoclonus is as followed;

- 0 = no myoclonus
- 1 = slight myoclonus (little contraction of a few muscle fibers e.g. of arm)
- 2 = modest myoclonus (contraction in diverse muscle groups e.g. muscles of face and foot)
- 3 = severe myoclonus (intensive contraction in 2 or additional groups of muscles e.g. whole body movement or adduction of a limb)

The data compared between Group D and M included age, mean weight, gender distribution, ASA status, hemodynamic factors (heart rate and mean blood pressure) and the incidence along with its severity. All the data was gathered on a p performa by the researchers themselves. The data was put in SPSS version 23 computer software and analyzed. Chi square test was applied on nominal data and continuous data was compared by applying Independent t test. P value ≤ 0.05 was reflected to be of statistical importance.

RESULTS

Age, weight, gender distribution and ASA status was not considerably dissimilar in Group D and M (p >0.05).Table-1

Table No.I: Baseline Data

Variable	Group D (n=50)	Group M (n=50)	P-Value
Age, years	38.50±10.33	40.04±10.10	0.453
Weight, Kg	54.12±13.63	57.14±12.74	0.255
Male / Female	29/21	27/23	0.687
ASA-I / ASA-II	39/11	45/15	0.362

Data was entered as mean ± S.D unless stated otherwise.

Table No.2: Hemodynamic Effects

Factor	Group D (n=50)	Group M (n=50)	P-Value
Heart Rate, Baseline	84.62±6.59	84.08±10.33	0.756
Heart Rate, after test drug injection	80.51±4.15	82.80±5.86	0.026
Heart Rate, at 0 min after intubation	75.21±3.75	80.96±5.09	<0.001
Heart Rate, at 1 min after intubation	78.10±4.17	89.11±7.29	<0.001
Heart Rate, at 3 min after intubation	75.84±3.84	83.60±6.43	<0.001
Heart Rate, at 5 min after intubation	73.94±2.85	81.88±4.95	<0.001
Mean BP, Baseline	101.32±5.67	99.82±4.95	0.162
Mean BP, after test drug injection	98.40±5.44	96.74±5.17	0.121
Mean BP, at 0 min after intubation	94.51±4.51	96.50±5.29	0.044
Mean BP, at 1 min after intubation	99.26±4.92	101.34±4.21	0.025
Mean BP, at 3 min after intubation	96.01±4.31	99.31±5.64	0.001
Mean BP, at 5 min after intubation	94.41±3.84	96.26±5.28	0.047

Data was entered as mean ± S.D.

There was no **significant** difference of heart rate and mean blood pressure before intubation between the two groups. There was statistically substantial fall in post intubation heart rate in Group D as paralleled to Group M (p<0.001). There was no decrease in post intubation heart rate as well as blood pressure in Group M. The decrease in mean arterial pressure was statistically noteworthy in Group D in comparison with Group M at 0, 1, 3 and 5 minutes post intubation (p value 0.044, 0.025, 0.001 and 0.047, respectively). Table-2.

There was no myoclonus seen in 26 (56%) of Group D patients and 9 (18%) in the Group M patients. Grade 1 myoclonus was seen 15 (30%) of Group D patients and 11 (22%) of Group M patients. Grade 2 myoclonus was observed in 8 (16%) of Group D patients and 23 (46%) of Group M patients and grade 3 myoclonus was observed in 1 (2%) of Group D patients and 7 (14%) of Group M patients. The change in the occurrence of myoclonus was statistically substantial (p <0.001). Table-3

Table No.3: Myoclonus Incidence, N (%)

Grade of Myoclonus	Group D (n=50)	Group M (n=50)	P-Value
0	26 (52)	9 (18)	<0.001
1	15 (30)	11 (22)	
2	8 (16)	23 (46)	
3	1 (2)	7 (14)	

DISCUSSION

Our study clearly suggested that dexmedetomidine is an effective agent in attenuating the hemodynamic stress response and incidence as well as severity of myoclonus caused by etomidate. Many other agents such as sufentanil and remifentanil have been tried for decreasing incidence of myoclonus[3,5]. Locus ceruleus has highest density of alpha 2 adrenoceptors which is the site of action for dexmedetomidine[13]. Activation of these receptors impedes the release of nor adrenalin which consequences in sedation and hypnosis. Other effects of dexmedetomidine are related to analgesia, anxiolysis and sympatholysis. Stress responses of endotracheal intubation and laryngoscopy are significantly attenuated by dexmedetomidine which decreases the doses of propofol and opioids[14].

Results of various studies[15-21] conducted around the world were in agreement with the results of our study. Dexmedetomidine at a dose of 1 µg /kg was given over 15 minutes prior to initiation of anesthesia, in the study performed by Menda et al[15]. They witnessed significant decrease in heart rate during intraoperative period as compared to the baseline value. Mizrak et al[16] found out that thiopental or dexmedetomidine is effective in decreasing the severity and occurrence of myoclonus after etomidate injection. The frequency of

myoclonus was around 34% in dexmedetomidine group, 36% in thiopental group while 64% in the control group. In a study conducted by Isitemiz et al[17], fentanyl (1 µg /kg) alone and the combination of fentanyl (0.5 µg /kg) and midazolam (0.015 mg /kg) were operative in decreasing the occurrence of myoclonus due to etomidate.

Gunes et al[18] compared midazolam with dexmedetomidine and found out that both the drugs work in dropping the occurrence of myoclonus caused by etomidate. Similar results were found out by Salman N et al[19] that both midazolam and dexmedetomidine are effective in reducing myoclonus incidence following etomidate injection but they also observed respiratory depression in the midazolam group. Sulaiman et al[20] calculated the properties of dexmedetomidine over the hemodynamic responses of endotracheal intubation and laryngoscopy. The found it to be effective in suppressing the hemodynamic stress responses. They administered 0.5 µg/kg dose of dexmedetomidine as infusion over ten minutes before the induction of anesthesia. Laun HF et al[21] used two different doses of dexmedetomidine i.e. 0.5 µg/kg and 1 µg/kg. Both doses were effective in reducing myoclonus occurrence but the incidence of adverse effects such as bradycardia was more with the higher dose.

CONCLUSION

In the patients who pre medicated with dexmedetomidine, the incidence as well as the severity of myoclonus was considerably lower as compared to the patients who were pre medicated with midazolam. Moreover, dexmedetomidine was a successful agent to attenuate, to a significant extent, the hemodynamic stress responses of intubation.

Author's Contribution:

Concept & Design of Study:	Liquat Ali
Drafting:	Muhammad Shahid
Data Analysis:	Malik Jamil Ahmed, Aamir Furqan.
Revisiting Critically:	Liquat Ali, Muhammad Shahid
Final Approval of version:	Liquat Ali

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Jackson Jr WL. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. Chest 2005;127(3):1031-8.
2. Oglesby AJ. Should etomidate be the induction agent of choice for rapid sequence intubation in the emergency department? Emerg Med J 2004; 21(6):655-9
3. Hueter L, Schwarzkopf K, Simon M, Bredle D, Fritz H. Pretreatment with sufentanil reduces myoclonus after etomidate. Acta Anaesth Scand 2003;47(4):482-4.
4. Hüter L, Schreiber T, Gugel M, Schwarzkopf K. Low-dose intravenous midazolam reduces etomidate-induced myoclonus: a prospective, randomized study in patients undergoing elective cardioversion. Anesth Analg 2007;105(5): 1298-302.
5. Kelsaka E, Karakaya D, Sarihasan B, Baris S. Remifentanil pretreatment reduces myoclonus after etomidate. J Clin Anesth 2006;18(2):83-6.
6. Van Keulen SG, Burton JH. Myoclonus associated with etomidate for ED procedural sedation and analgesia. Am J Emerg Med 2003;21(7):556-8.
7. Ruth WJ, Burton JH, Bock AJ. Intravenous etomidate for procedural sedation in emergency department patients. Acad Emerg Med 2001; 8(1):13-8.
8. Schwarzkopf KR, Hueter L, Simon M, Fritz HG. Midazolam pretreatment reduces etomidate-induced myoclonic movements. Anaesth Intens Care 2003;31(1):18.
9. Guler A, Satilmis T, Akinci SB, Celebioglu B, Kanbak M. Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg 2005;101(3):705-9.
10. Choi JM, Choi IC, Jeong YB, Kim TH, Hahm KD. Pretreatment of rocuronium reduces the frequency and severity of etomidate-induced myoclonus. J Clin Anesth 2008;20(8):601-4.
11. Ramsay MA, Newman KB, Leeper B, Hamman BL, Hebeler Jr RF, Henry AC, et al. Dexmedetomidine infusion for analgesia up to 48 hours after lung surgery performed by lateral thoracotomy. In Baylor University Medical Center Proceedings. Taylor & Francis 2014;27(1):3-10.
12. Dey S, Kumar M. Comparison of pretreatment with dexmedetomidine with midazolam for prevention of etomidate-induced myoclonus and attenuation of stress response at intubation: A randomized controlled study. J Anaesthesiol Clin Pharmacol 2018;34(1):94.
13. Clayton EC, Rajkowski J, Cohen JD, Aston-Jones G. Phasic activation of monkey locus ceruleus neurons by simple decisions in a forced-choice task. J Neurosci 2004;24(44):9914-20.
14. Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S. Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation. Drugs in R & D. 2006;7(1):43-52
15. Menda F, Koner O, Sayin M, Ture H, Imer P, Aykac B. Dexmedetomidine as an adjunct to anesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients

undergoing fast-track CABG. Annals Cardiac Anaesth 2010;13(1):16.
16. Mizrak A, Koruk S, Bilgi M, Kocamer B, Erkutlu I, Ganidagli S, Oner U. Pretreatment with dexmedetomidine or thiopental decreases myoclonus after etomidate: a randomized, double-blind controlled trial. J Surg Res 2010;159(1): e11-6.
17. Isitemiz I, Uzman S, Toptaş M, Vahapoglu A, Gül YG, Inal FY, Akkoc I. Prevention of etomidate-induced myoclonus: Which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study. Medical science monitor: Int Med J Exp Clin Res 2014;20:262.
18. Gunes Y, Aktolga S, Gündüz M, Isik G. A comparison of midazolam or dexmedetomidine for the prevention of myoclonic movements and injection pain following etomidate injection: 9AP3–8. Eur J Anaesthesiol 2010;27(47):148.
19. Salman N, Gurbuz HA, Oguzalp H, Ucar HI, Yorgancioglu C, Sekerci S. Comparison of dexmedetomidine and midazolam in prevention of myoclonus occurring due to etomidate in coronary bypass surgery. J Cardiovasc Surg 2013;1:52-6.
20. Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H, Gandham R. The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Annals Cardiac Anaesth 2012; 15(1):39.
21. Luan HF, Zhao ZB, Feng JY, Cui JZ, Zhang XB, Zhu P, Zhang YH. Prevention of etomidate-induced myoclonus during anesthetic induction by pretreatment with dexmedetomidine. Braz J Med Biol Res 2015;48(2):186-90.
22. Wujtewicz M, Maciejewski D, Misiołek H, Fijałkowska A, Gaszyński T, Knapik P, Lango R. Use of dexmedetomidine in the adult intensive care unit. Anaesthesiol Intens Ther 2013;45(4):235-40.