



Original article

A Comparative Study Of Etomidate And Midazolam Induction In Patients Undergoing Coronary Artery Bypass Graft Surgery

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ABSTRACT

Background : To compare the effects of etomidate and midazolam induction on hemodynamic changes during laryngoscopy and intubation in patients undergoing elective Coronary Artery Bypass Graft (CABG) surgery. **Method and Material :** A total of 70 patients with triple vessel coronary artery disease, aged between 30 to 60 years undergoing CABG surgery were included in this prospective, comparative and randomized study and divided into two groups; group E (Etomidate group, n=35, 0.3mg/kg) and group M (Midazolam group, n=35, 0.15mg/kg). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI) and systemic vascular resistance index (SVRI) were recorded at various time points starting from preinduction till 10 minutes after intubation. **Statistical Analysis:** The SPSS, version 20 for Windows statistical software package (SPSS inc., Chicago, Illinois, USA). Results were analyzed using student's t-test and paired t-test. **Results:** In group M after induction HR increased (P <0.05); SBP and MAP decreased (P <0.05), while at 1 min after tracheal intubation the values of HR increased and SBP decreased (p <0.05). Whereas in group E, HR and SBP increased remarkably at 1 min after intubation (P < 0.001 and P <0.05, respectively). Both the groups showed no significant change in DBP, CO and CI before and after intubation. There was significant decrease in CVP in both the groups (P <0.001). Group M showed significant decrease in SVRI (P <0.001). **Conclusion :** In comparison with Etomidate, Midazolam used for the induction of anesthesia in CABG surgery was more effective in preventing the adverse cardiovascular response to laryngoscopy and intubation.

KEYWORDS: Anesthesia induction, Coronary artery bypass graft surgery, Triple vessel coronary artery disease.

INTRODUCTION

Whether during the traditional on-pump CABG (coronary artery bypass graft) surgery or the newer off-pump CABG surgery, a number of drugs have been used in an attempt to attenuate the undesirable hemodynamic responses to laryngoscopy and intubation. These responses occur 30 seconds after intubation, lasting for less than 10 minutes and are of sympathetic in origin [1]. Many patients with coronary artery disease experience episodes of myocardial ischemia during intubation especially with decreased reserve for coronary blood flow and when no specific prevention is undertaken [2]. Many authors have performed studies regarding induction of anesthesia with agents such as thiopentone, etomidate, midazolam, propofol, and ketamine with various results.

Use of etomidate is advocated in patients with compromised cardiopulmonary function, because of its less cardiovascular and respiratory depressant effects and lack of histamine release. With Etomidate^(R)-Lipuro, some adverse effects, eg-phlebitis, thrombosis have been nearly eliminated while myoclonus have been substantially reduced. While water solubility of midazolam maleate permits its formulation in a less irritating vehicle as well as the short duration of action compare it favorably with other induction agents. Some authors have concluded in their study that the rapid onset of midazolam and its modest effect on hemodynamic parameters make it a safe and efficacious induction agent in patients with ischemic heart disease [3].

The present study was designed to compare Etomidate and Midazolam for induction in regard to hemodynamic stability and minimizing intubation stress response in CABG surgery.

MATERIALS AND METHODS

A power analysis from various previous studies revealed a sample size of 31 patients per group was required to achieve a power of 80% and at alpha error of 0.05 for detection of minimum desired hemodynamic change in mean arterial pressure (8 mmHg difference) [4]. It was decided to take 35 patients in each group.

A total of 70 patients aged between 30 to 60 years with triple vessel coronary artery disease and left ventricular ejection fraction >35%; presenting for elective CABG surgery, were included in this prospective, comparative and randomized study, after approval from the institutional ethics committee and written informed consent from the patients. The Study was conducted between January 2014 to April 2014. Patients with valvular heart disease, congestive cardiac failure, known adrenal insufficiency, severe systemic diseases other than hypertension and diabetes, and patients fitting in the criteria of difficult intubation (Mallampati grade 3 & 4) were excluded from the study. We also excluded the patients in whom total duration of laryngoscopy and intubation was more than 90 seconds and one time laryngoscopy and intubation was more than 15 seconds.

The patients were randomized into one of the two groups of 35 patients each, by the sealed envelope technique, depending on the study drug (Group E - Etomidate 0.3 mg/kg, Group M - Midazolam 0.15 mg/kg). Blocks of 10 sealed opaque envelopes, 5 Etomidate and 5 Midazolam were prepared and mixed in a box. An envelope was picked randomly and opened once an eligible patient had consented. They were then randomly assigned to anesthetists experienced in giving anesthesia for CABG surgeries. On average 4-5 patients were enrolled per week. A total of 35 patients in the group E and 35 patients in the group M were completed in a span of 4 months.

All preoperative cardiac medications were continued till the morning of the surgery. Patients were premedicated with Inj. morphine 0.1mg/kg and Inj. promethazine 0.5mg/kg i.m. 45 min. prior to surgery. Inside the operation theatre 5-lead ECG and pulse oxymeter was connected then femoral artery cannulation was done for invasive blood pressure monitoring. Central venous catheter and pulmonary artery catheter was placed via right internal jugular vein. All cannulation were performed under local anesthetics. Inj. Fentanyl (3µg/kg); was given i.v. slowly over one minute. After a period of five minutes, baseline parameters in the form of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI) and systemic vascular resistance index (SVRI) were recorded. The cardiac output was measured using thermodilution method via pulmonary artery catheter.

Induction of anesthesia was performed using either Inj. Etomidate (0.3mg/kg) or Inj. Midazolam (0.15mg/kg). The drug was administered in small doses over a period of 60-90 seconds. Muscle relaxation for intubation was facilitated by Inj. Rocuronium 0.9mg/kg. Positive pressure ventilation was

done with 100% oxygen for a period of three minutes. HR, SBP, DBP, MAP & CVP were recorded at 1 min, 2 min and 3 min and CO, CI and SVRI were recorded at 3 min after giving the study drug for induction. 3 min after induction endotracheal intubation was performed. Again the HR, SBP, DBP, MAP & CVP were recorded at 1 min, 3 min, 5 min and 10 min after intubation and CO, CI, SVRI were recorded at 3 min after intubation. Surgery or any other manipulations were not allowed to commence till ten minutes after intubation, which was the end point of our study. Throughout this period mechanical ventilation was performed with 100% oxygen to maintain an end-tidal carbon dioxide between 35 and 40 mmHg.

STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS, version 20 for Windows statistical software package (SPSS inc., Chicago, Illinois, USA). The Categorical data i.e. sex was presented as numbers (percent) and was compared among groups using Chi square test. Demographic data (i.e. age, weight) and hemodynamic variables were presented as mean and standard deviation. To evaluate whether there was a statistically significant difference; comparison between the groups, was done by using student's t-test and comparison within the groups was performed by using paired t-test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.001.

RESULTS

Both the groups were comparable with regard to demographic data in terms of age, sex and weight [Table 1]. Baseline hemodynamic data were comparable between both the groups [Table 2]. After induction heart rate increased (+6%) [Table 3], while systolic and mean arterial blood pressure decreased (-6% and -4% respectively) in midazolam group ($p < 0.05$) [Table 4]. After intubation both the groups showed significant increase in heart rate (+18%; $p < 0.001$ in etomidate group and +8%; $p < 0.05$ in midazolam group) [Table 3]. At 1 minute after intubation there was significant increase in systolic blood pressure (+3%) in etomidate group and decrease (-5%) in midazolam group ($p < 0.05$ in each group).

Intergroup comparison between both the groups revealed that at 1 minute after intubation both heart rate ($p < 0.05$) and systolic blood pressure ($p < 0.001$) were significantly increased in etomidate group [Table 4]. Central venous pressure significantly decreased in both the groups, before and after intubation ($p < 0.001$) [Table 5]. Diastolic blood pressure, mean arterial pressure, cardiac output and cardiac index remained comparable to baseline during induction and intubation in both the groups. Midazolam group showed significant decrease in systemic vascular resistance index throughout the study period ($p < 0.001$) [Table 5]. Myoclonus was observed in 2 patients in etomidate group while 4 patients complained pain on injection with midazolam. 2 patients suffered from bradycardia and 1 patient from severe hypotension after midazolam induction.

Table 1: Patient demographic data expressed as mean ± S.D.

Demographic Data	Group E (n=35)	Group M (n=35)	Significance (P value)
Age (yrs)	55.31± 6.12	53.06± 6.39	NS (0.14)
Sex (M/F)	29/6	25/10	NS (0.39)
Weight (kgs)	63.94± 10.32	65.03± 10.33	NS (0.66)

Qualitative data (i.e. sex) is presented as numbers and quantitative data (i.e. age and weight) are presented as mean ± SD. NS = non significant, S= significant, $p<0.05$ - significant.

Table 2: Comparison of Mean Baseline Variables in both the groups

Baseline Hemodynamic parameters	Group E	Group M	Significance (P value)
Heart rate (beats/min)	89.94±16.51	89.09±17.94	NS (0.83)
Systolic Blood pressure (mmHg)	143.17±18.92	141.66±17.65	NS (0.73)
Diastolic Blood pressure (mmHg)	90.34±15.76	84.94±14.12	NS (0.14)
Mean arterial Pressure (mmHg)	107.94±16.10	103.80±12.69	NS (0.23)
Central Venous Pressure (mmHg)	13.97±4.00	13.66±3.21	NS (0.72)
Cardiac Output (L/min)	5.92±1.97	5.07±1.59	NS (0.05)
Cardiac index (L/min/m ²)	3.29±1.09	2.87±0.88	NS (0.07)
Systemic Vascular Resistance Index (Dyne/sec.cm-5/m ²)	2396.10±804.83	2261.40±505.19	NS (0.40)

Data presented as mean ± SD. comparison between the groups by student's t-test and comparison within the groups by paired t- test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.001. NS = non significant, S= significant, $p<0.05$ - significant

Table 3: Comparison of Mean change in Heart Rate from the baseline value at various time interval between both the groups

Hemodynamic variable	Group E (N=35)		Group M (N=35)		Intergroup Comparison (between E and M) Significance (P value)
	Mean change± SD	Significance (P value)	Mean change± SD	Significance (P value)	
HR (beats/min)					
1 min after induction	1.46±8.22	NS (0.30)	3.09±7.81	S (0.03)	NS (0.40)
2 min after induction	2.86±11.32	NS (0.15)	4.97±10.12	S (0.01)	NS (0.41)
3 min after induction	3.40±11.69	NS (0.09)	4.91±10.92	S (0.01)	NS (0.58)
1 min after intubation	16.49±15.26	HS (0.001)	6.97±15.56	S (0.01)	S (0.01)
3 min after intubation	14.74±14.90	HS (0.001)	8.77±17.85	S (0.01)	NS (0.13)
5 min after intubation	10.74±15.86	HS (0.001)	6.46±18.80	S (0.05)	NS (0.31)
10 min after intubation	6.03±14.89	S (0.02)	3.29±15.25	NS (0.21)	NS (0.45)

Data presented as mean ± SD. comparison between the groups by student's t-test and comparison within the groups by paired t- test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.001. NS = non significant, S= significant, $p<0.05$ - significant

Table 4: Comparison of Mean change in hemodynamic variables from the baseline value at various time interval between both the groups

Hemodynamic variable	Group E (N=35)		Group M (N=35)		Intergroup Comparison (between E and M)
	Mean change± SD	Significance (P value)	Mean change± SD	Significance (P value)	Significance (P value)
Systolic Blood Pressure (mmHg)					
1 min after induction	-0.83±4.57	NS (0.29)	-8.03±26.67	NS (0.08)	NS (0.14)
2 min after induction	-1.77±5.64	NS (0.07)	-6.54±14.01	S (0.01)	NS (0.07)
3 min after induction	-2.06±10.27	NS (0.24)	-8.37±13.49	S (0.01)	S (0.03)
1 min after intubation	4.03±11.22	S (0.04)	-7.00±15.06	S (0.01)	HS (0.001)
3 min after intubation	-0.69±15.71	NS (0.80)	-9.03±14.94	HS (0.001)	S (0.01)
5 min after intubation	-7.57±17.20	S (0.01)	-11.57±16.04	HS (0.001)	NS (0.32)
10 min after intubation	-11.31±13.36	HS (0.001)	-13.83±13.43	HS (0.001)	NS (0.44)
Diastolic Blood Pressure (mmHg)					
1 min after induction	-0.77±4.14	NS (0.28)	-0.06±14.02	NS (0.98)	NS (0.77)
2 min after induction	-1.29±4.19	NS (0.08)	-3.60±13.25	NS (0.12)	NS (0.33)
3 min after induction	-1.40±7.69	NS (0.29)	-2.66±13.07	NS (0.24)	NS (0.63)
1 min after intubation	-0.37±15.82	NS (0.89)	0.71±13.61	NS (0.76)	NS (0.76)
3 min after intubation	-3.11±14.87	NS (0.22)	0.46±15.46	NS (0.86)	NS (0.33)
5 min after intubation	-2.31±15.37	NS (0.38)	-0.74±16.44	NS (0.79)	NS (0.68)
10 min after intubation	-3.49±13.46	NS (0.13)	-2.143±14.76	NS (0.40)	NS (0.35)
Mean Arterial pressure (mmHg)					
1 min after induction	-0.80±3.52	NS (0.19)	-2.71±12.68	NS (0.21)	NS (0.39)
2 min after induction	-1.43±3.74	NS (0.03)	-4.51±11.94	S (0.03)	NS (0.57)
3 min after induction	-1.54±7.40	NS (0.23)	-4.57±11.62	S (0.03)	NS (0.20)
1 min after intubation	1.11±12.96	NS (0.61)	-1.77±11.79	NS (0.38)	NS (0.33)
3 min after intubation	-1.86±13.25	NS (0.11)	-2.63±13.25	NS (0.25)	NS (0.81)
5 min after intubation	-4.51±14.84	NS (0.08)	-4.60±14.14	NS (0.06)	NS (0.97)
10 min after intubation	-6.97±11.58	S (0.001)	-6.29±11.91	S (0.004)	NS (0.81)

Data presented as mean ± SD. comparison between the groups by student's t-test and comparison within the groups by paired t- test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.001. NS = non significant, S= significant, *p*<0.05- significant

Table no.5: Comparison of Mean change in hemodynamic variables from the baseline value at various time interval between both the groups

Hemodynamic variable	Group E (N=35)		Group M (N=35)		Intergroup Comparison (between E and M)
	Mean change± SD	Significance (P value)	Mean change± SD	Significance (P value)	Significance (P value)
Central venous pressure (mmHg)					
1 min after induction	-0.83±1.89	S (0.01)	-0.54±1.15	S (0.01)	NS (0.44)
2 min after induction	-1.11±1.94	HS (0.001)	-0.86±1.26	HS (0.001)	NS (0.52)
3 min after induction	-1.50±2.09	HS (0.001)	-1.14±1.42	HS (0.001)	NS (0.41)
1 min after intubation	-1.31±1.88	HS (0.001)	-1.11±1.41	HS (0.001)	NS (0.63)
3 min after intubation	-1.39±1.84	HS (0.001)	-1.09±1.31	HS (0.001)	NS (0.43)
5 min after intubation	-1.28±1.77	HS (0.001)	-0.94±1.37	HS (0.001)	NS (0.38)
10 min after intubation	-1.22±1.73	HS (0.001)	-0.91±1.40	HS (0.001)	NS (0.42)
Cardiac output (L/min)					
3 min after induction	-0.12±1.27	NS (0.59)	-0.15±1.06	NS (0.40)	NS (0.90)
3 min after intubation	0.57±1.47	NS (0.03)	0.31±1.28	NS (0.16)	NS (0.44)
Cardiac Index (L/min/m ²)					
3 min after induction	-0.11±0.72	NS (0.39)	-0.11±0.60	NS (0.30)	NS (0.10)
3 min after intubation	0.29±0.83	NS (0.05)	0.18±0.72	NS (0.15)	NS (0.57)
Systemic Vascular Resistance Index (Dyne/sec.cm-5/m ²)					
3 min after induction	111.60±436.00	NS (0.14)	-173.80±234.96	HS (0.001)	HS (0.001)
3 min after intubation	166.60±494.45	NS (0.05)	-259.23±310.36	HS (0.001)	HS (0.001)

Data presented as mean ± SD. comparison between the groups by student's t-test and comparison within the groups by paired t- test. Probability was considered to be significant if less than 0.05 and highly significant if less than 0.001. NS = non significant, S= significant, HS = highly significant, *p*<0.05- significant, *p*<0.001- highly significant.

DISCUSSION

A hemodynamic response of increased heart rate and blood pressure to manipulation in the area of the larynx by means of laryngoscopy and intubation is transient but dangerous, especially in patients with poor cardiac reserve leading to myocardial ischemia and subsequently various types of dysrhythmias [5]. A wide variety of anesthetic drugs are in practice these days, which have been proved hemodynamically stable in cardiac patients by various studies conducted by different authors at different time points.

Induction of anesthesia with etomidate in cardiac patients results in stable hemodynamics with no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, or pulmonary and systemic vascular resistance [6]. Etomidate's hemodynamic

stability may be due to its lack of effect on the sympathetic nervous system and also on baroreceptor function, [7] but because of the same, etomidate does not block sympathetic responses to laryngoscopy [8,9]. Pain on injection, venous irritation have been abolished by new fat emulsion of etomidate (Medium chain triglyceride and soya bean named Etomidate-Lipuro [10,11]. Apart from this most recent studies have demonstrated only a transient decrease in serum cortisol levels after a single induction dose of etomidate, which is not clinically significant [12].

On the other hand Midazolam which is a benzodiazepine, is usually administered prior to surgery, to provide anxiolysis and sedation. Various studies conducted regarding the cardiovascular effects of Midazolam have yielded conflicting results. Surprisingly some authors have reported enhanced cardiovascular stability with Midazolam in their studies whereas some concluded that the rapid action of midazolam maleate and its modest effects on hemodynamic

parameters, make it a safe and efficacious induction agent in patients with ischemic heart disease [3].

Though there is extensive literature which proved Etomidate a hemodynamically stable drug with minimum adverse effects for anesthesia induction in patients with ischemic heart disease, but some recent studies suggested Midazolam to be more efficacious in improving overall cardiac performance by reducing after load. The present study is one more attempt to assess both the drugs and to validate the previous results, hence aiming to compare the effectiveness of Etomidate and Midazolam induction in attenuation of the adverse hemodynamic responses to laryngoscopy and endotracheal intubation as well as to note any significant side effects caused by the drugs.

The mean baseline pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, central venous pressure, cardiac output, cardiac index and systemic vascular resistance index were similar in both the groups.

After induction Etomidate maintained hemodynamic stability through preservation of both sympathetic activity and autonomic reflexes while Midazolam group showed significant fall in systolic blood pressure and rise in heart rate due to decrease in vascular resistance. Etomidate group showed significant increase in heart rate and systolic blood pressure after intubation as a result of sympathetic stimulation due to laryngoscopy and intubation. But this was not clinically significant and none of our patient showed visible ST segment changes. The comparison of mean change in heart rate and systolic blood pressure from the baseline in both the groups shows that at 1 min after intubation the rise in Etomidate group was significantly higher than Midazolam group. Similar increase in heart rate, after intubation, was also noted by Raveen et al [4] and Sanal Bas et al [13] in their studies.

Raveen et al [4] compared the hemodynamic effects of anesthesia induction with etomidate, thiopentone, propofol, and midazolam in patients with coronary artery disease and left ventricular dysfunction (ejection fraction < 45%) scheduled for elective CABG surgery. There was a significant decrease in the heart rate, mean arterial pressure and cardiac index after induction in all four groups. The midazolam group was the most effective in preventing intubation stress with non significant change from baseline values in heart rate (+4%) and mean arterial pressure (-1%) after intubation. While the etomidate group was the least effective of all the groups in minimizing stress response, with significant increase from baseline in both heart rate (+15%) and mean arterial pressure (+9%) at 1 minute after intubation. Similar results were also found in our study.

Sanal Bas et al [13] compared the hemodynamic effects of Thiopental, Propofol, Etomidate and Midazolam on induction of anesthesia, laryngoscopy and endotracheal intubation in hypertensive patients undergoing CABG surgery. The change in heart rate was not significant between the groups but in the Etomidate group increase in systolic blood pressure during laryngoscopy and tracheal intubation was statistically significant. Similar increase in systolic blood pressure after intubation was also found in our study.

Reves et al [3] studied the changes in hemodynamic parameters in ten patients with symptomatic ischaemic heart

disease after anesthesia induction with intravenous midazolam maleate 0.2 mg/kg. Midazolam significantly reduced systemic systolic/diastolic pressure and mean blood pressure. The heart rate increased after induction whereas stroke volume and systemic vascular resistance index were significantly reduced. These changes were similar to our results.

Messina et al [14] studied forty patients undergoing coronary artery bypass grafting, to evaluate the effects of midazolam on LV pump performance and contractility. Midazolam did not affect cardiac index. Heart rate, mean arterial pressure, central venous pressure, systemic and pulmonary vascular resistance were reduced as well as the afterload. Similar decrease in systemic vascular resistance was also noted in our study. Thereby reducing afterload, Midazolam caused improvement in overall cardiac performance.

The maintenance of hemodynamic stability during induction of anesthesia is not only dependent on the basal "tone" of the autonomic nervous system but is also importantly influenced by baroreceptor reflex regulation of autonomic outflow influencing cardiac function and peripheral vascular resistance. According to a study conducted by Ebert et al [7] etomidate maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes. This theory can explain our findings regarding to increased heart rate and arterial blood pressures following intubation in etomidate group.

On the other hand the most consistent hemodynamic changes following administration of midazolam in this study and in others previously recorded are a small increase in heart rate and decrease in systemic blood pressure. Theoretically, these hemodynamic changes may be unsuitable for patients with ischemic heart disease because of increased myocardial oxygen consumption and decreased coronary blood flow. However, in our study no patient developed new ECG ischemic changes following midazolam, suggesting that the minimal hemodynamic changes did not add to preexisting myocardial ischemia.

In our study both the groups showed significant fall in CVP which might be due to either inadequate intravenous fluid administration during the study period or intravenous infusion of peripheral vasodilators like Inj. Nitroglycerine, which is routinely given in CABG surgeries to improve myocardial perfusion. In Midazolam group fall in CVP might be a result of peripheral vasculature dilatation, which, at the same time also results in fall in systemic vascular resistance. The hemodynamic changes brought about by anesthesia induction in our study consisted of a non significant decrease in CO, which might have been caused by decrease in arterial pressure while intubation caused no significant rise in CO which might be attributed to increase in heart rate as well as arterial pressure due to sympathetic stimulation.

Because there are no certain rules in anesthesia drugs to be used in cardiac surgeries, the choice should be based on considerations like they shall not make sudden and massive hemodynamic changes, shall not cause any adverse response to tracheal intubation and surgical stimulation as well as ischemic complications shall be reduced. From this point of view, when looking at statistical difference between both the groups we can clearly make out the inference that the more

trustable anesthesia induction method in patients undergoing CABG could be with midazolam besides fentanyl and rocuronium in laryngoscopy and endotracheal intubation.

CONCLUSION

To conclude, All the above mentioned facts suggest that Midazolam was more effective than Etomidate in attenuating the adverse hemodynamic changes in response to laryngoscopy and intubation in patients with triple vessel coronary artery disease undergoing elective CABG surgery.

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