Original Article

Comparing the Hemodynamic Effects of Midazolam, Etomidate, and Propofol following Anesthesia Induction in Coronary Artery Bypass Graft Surgery: A Double-Blind Randomized Clinical Trial

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Abstract

Background: *Hemodynamic disorders during anesthesia lead to complications. To reduce hemodynamic complications, this study was conducted to compare midazolam, etomidate, and propofol following anesthesia induction in patients undergoing coronary artery bypass grafting surgery (CABG).*

Methods: *A double-blind, randomized clinical trial was conducted involving 90 patients with coronary artery disease. These patients were randomly assigned to 1 of 3 groups receiving propofol, etomidate, or midazolam. Hemodynamic variables, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), and heart rate (HR), were measured at baseline, before intubation, and 1 and 5 minutes after intubation.*

Results: *Ninety patients with coronary artery disease (mean age: 60.83 y) were included in the study. Women and men comprised 74.4% and 25.6% of the study population. HR, SBP, DBP, and MABP exhibited significant decreases in all 3 groups after intubation. The etomidate group demonstrated the least change in SBP ($P<0.001$) and MABP ($P<0.001$), followed by the midazolam group. Concerning HR, the least change was observed in the midazolam group, followed by the propofol group ($P=0.688$). After intubation, blood pressure increased almost equally in the etomidate and midazolam groups compared with the levels during intubation. In contrast, the propofol group exhibited a downward trend in blood pressure during intubation, a significant difference across all 3 groups ($P<0.001$).*

Conclusion: *This study, conducted on candidates for CABG, demonstrated that anesthesia induction with etomidate and midazolam resulted in less variation in hemodynamic variables compared with propofol.*

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Introduction

Coronary artery disease represents the foremost cause of mortality within the spectrum of cardiovascular disease across all age groups.[1] The mortality rate attributable to cardiovascular disease is notably high in Iran, where out of every 700 to 800 daily deaths, 317 are ascribed to this group of diseases.[2] Conventional treatments often lack efficacy in terms of improving the quality of life for patients with coronary artery disease.[3] In response, coronary artery bypass grafting surgery (CABG) is considered a pivotal approach. The primary objective of this surgical procedure is to extend life expectancy while mitigating chest pain symptoms.[4] Nevertheless, a considerable proportion of CABG candidates present with underlying diseases and widespread atherosclerosis, rendering them susceptible to vascular complications and hemodynamic disorders.[5]

Hemodynamic instability during the anesthesia phase carries adverse implications for systemic blood circulation and tissue oxygenation, particularly for vital organs such as the brain, kidneys, and liver.[6] Post-CABG complications stemming from hemodynamic instability are considerable. Long-term outcomes reveal an association between increased pulse pressure during CABG and diminished patient survival. Moreover, an increase of 20 mm Hg in blood pressure is linked to a 50% elevation in the risk of developing renal insufficiency.[7,8] Consequently, during CABG, a fundamental objective is to minimize sympathetic responses to stimuli, including laryngoscopy, intubation, skin incision, and sternotomy, and to achieve a delicate equilibrium between the resultant hemodynamic fluctuations throughout the procedure. This equilibrium is pivotal for maintaining optimal myocardial oxygen supply and demand.[9]

Furthermore, given that anesthetic agents invariably induce specific hemodynamic changes, there is a perpetual endeavor to employ drugs for anesthesia induction and maintenance that minimize patient complications and induce the fewest cardiovascular and hemodynamic perturbations.[10] Two well-recognized anesthetic agents, propofol and etomidate, are routinely used for anesthesia induction in cardiac surgery, and each is characterized by distinct clinical attributes.[11] Still, these agents are not without their share of side effects.[12-14] Another frequently administered drug is midazolam, which is suitable for both anesthesia induction and maintenance. The impact of midazolam on the cardiovascular system, encompassing blood pressure, heart rate (HR), and cardiac output, is minimal, while it exerts limited influence on coronary artery flow, reduces myocardial oxygen consumption, and preserves myocardial contractility, making it an appropriate choice for anesthesia induction in patients with cardiovascular disease.[15,16] Furthermore, its side effects are relatively modest.[17]

Considering the paramount significance of hemodynamic fluctuations during CABG and their profound ramifications for postoperative outcomes, the present study was formulated to investigate and compare the hemodynamic effects of 3 drugs, namely propofol, etomidate, and midazolam, during CABG. The primary goal of the study was to generate valuable data that could contribute to improved anesthesia techniques and ultimately minimize complication rates in this surgical setting.

Methods

This double-blind, randomized clinical trial was conducted at Farshchian Heart Hospital in the Iranian city of Hamedan in 2022. The target population was composed of individuals eligible for CABG at this hospital. The requisite sample size was determined to be a minimum of 30 participants in each group based on mean arterial blood pressure (MABP), totaling 90 individuals, based on the findings of prior research.[18] This determination was made while maintaining a type I error of 0.05 and a test power of 80% via the utilization of Stata 11 software. Thirty participants were randomly allocated to each of the 3 groups (Figure 1).

Inclusion criteria encompassed individuals aged between 40 and 70 years, classified under the American Society of Anesthesiologists classes II and III, and identified as suitable candidates for CABG. Patients were excluded if they had diabetes, required emergency surgery, had known hypersensitivity to anesthetic agents, or declined to provide informed consent for participation in the study.

This study was conducted with the formal approval of the Ethics Committee of the Research Deputy at Hamadan University of Medical Science (codes: IR.UMSHA.REC.1400.072 and IRCT20120215009014N391). Before the study commenced, written informed consent was obtained from all the participants. They were assured that the drugs used were well-established, with minimal side effects, as documented in established reference textbooks. The patients also received reassurances that their personal information would remain confidential, and their data would be used solely for statistical purposes. Participation in the study was voluntary, and refusal to participate did not result in any disturbance to the patient's care.

The researcher filled out a checklist, which included sex, age, body mass index, ejection fraction, MABP, systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR.

The participants were randomly assigned to 1 of the 3 groups through computerized sequence generation, ensuring a double-blind study design. In view of the structural similarities among the 3 drugs, the participants remained unaware of the specific drug administered. Furthermore, the medications were prepared by personnel not directly involved in the study, following the appropriate dosage guidelines. These prepared medications were then supplied

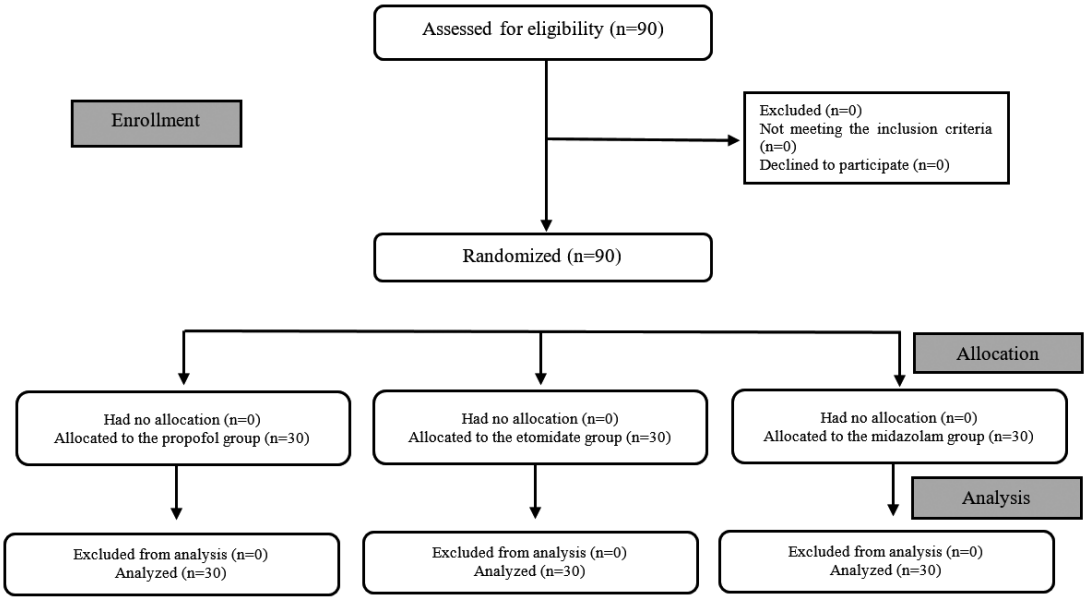

Figure 1. The image presents the flowchart of patient enrollment in the 3 groups.

to the anesthesiologist, ensuring adherence to the intended treatment protocol while maintaining blinding within the study. The randomization process was conducted by an individual external to the study. Consequently, those responsible for data collection and subsequent analyses were double-blinded to this allocation process.

All the patients were given a preoperative visit the night before surgery, and the demographic information of eligible participants was collected. The patients were subjected to an 8-hour preoperative fasting period (NPO). For premedication, the participants were administered 1 mg of lorazepam the night before the operation and an additional dose 2 hours preoperatively. One hour before surgery, 5 mg of morphine was intramuscularly injected for all the patients. Ringer's solution (500 mL) was administered to all the patients 1 hour before anesthesia induction. The subjects also received narcotic sufentanil (1 µg/kg), cisatracurium (0.2 mg/kg), and midazolam (2 mg) as a sedative before anesthesia induction. During anesthesia, additional sedatives were administered. Specifically, the first group received midazolam (0.15 mg/kg), the second group received etomidate (0.2 mg/kg), and the third group received propofol (1.5 mg/kg).

In the operating room, standard monitoring, including continuous electrocardiography, was instituted, and arterial line catheters were uniformly placed for all the patients. SBP, DBP, MABP, and HR were recorded before anesthesia induction, following intubation (3 minutes after induction), and 5 minutes after intubation. Ultimately, these variables were analyzed to compare the hemodynamic stability and drug performance within each group.

The normality of data distribution was ascertained through the Kolmogorov-Smirnov test and tests of equality of variances (Levene's test). Subsequently, paired *t*, one-way ANOVA, and repeated measure ANOVA tests were employed to compare variable means. Additionally, a χ^2 statistic was utilized to assess the frequency differences across the 3 groups. Data analysis was executed using IBM SPSS statistical software, version 16 (Build 1.0.0.1347; IBM, New York, USA), with a 95% confidence interval. An intention-to-treat approach was adopted for the analysis.

Results

This double-blind clinical trial randomly divided 90 patients undergoing CABG into 3 groups of 30 participants each, receiving propofol, etomidate, or midazolam. Women and men accounted for 74.4% and 25.6% of the study population, with a mean age of 60.83 years.

Table 1 presents a comparison of baseline hemodynamic variables before anesthesia induction and demographic characteristics across the 3 groups. The findings revealed that the studied patients did not exhibit statistically significant differences concerning their demographic characteristics or key hemodynamic parameters, such as HR (*P*=0.252), SBP (*P*=0.877), DBP (*P*=0.057), and MABP (*P*=0.368). Nevertheless, distinctions were observed concerning ejection fraction (P=0.006). To account for the influence of differing ejection fractions at baseline, the variable was treated as a covariate in subsequent analyses.

Table 2 presents the frequency of individuals in the various drug groups that deviated from the protocol established for this study. The results indicated that, in addition to the specified primary drug, several patients received additional medications (vasopressors) due to hemodynamic fluctuations. Notably, the propofol group exhibited the

highest incidence of protocol violations, which proved to be statistically significant compared with the other groups (P=0.003).

Table 3 provides both intra- and intergroup comparisons of HR, SBP, DBP, and MABP among the 3 drug groups. The results revealed that, over the recorded time intervals, HR variations exhibited no significant differences across the drug groups (P=0.065). However, distinctive trends were observed in SBP, DBP, and MABP across the groups throughout the specified time points (P<0.001). Moreover, in the intergroup comparisons, the impact of the administered drug demonstrated variations in the alterations of mean SBP (P<0.001) and MABP (P<0.001). These findings are further elucidated in Figure 2.

Table 4 presents intragroup mean comparisons of HR, SBP, DBP, and MABP concerning the baseline values across the study groups. The etomidate group exhibited a significant difference in HR compared with the baseline at all the recorded time points (P≤0.001). Additionally, a significant variance was identified in SBP and DBP within the propofol group at all the observed time intervals in contrast to the baseline measurements (P<0.001). In terms of MABP, both the propofol and midazolam groups displayed significant discrepancies compared with the baseline at all the recorded time points (P≤0.001).

Table 1. Comparisons of the hemodynamic basal variables before the induction of anesthesia and demographic variables among the 3 drug groups

Variable	Groups			P
	Propofol (n=30)	Etomidate (n=30)	Midazolam (n=30)	
Sex (%)				
Female	23 (76.7)	24 (80.0)	20 (66.7)	0.474
Male	7 (23.3)	6 (20.0)	10 (33.3)	0.474
Age (y)	58.81±9.72	61.51±8.50	62.20±8.77	0.305
BMI (kg/m$^{2)}$	26.88±2.90	26.22±4.00	27.00±4.61	0.676
EF (mg/dL)	48.81±7.01	41.28±10.71	44.52±8.19	0.006
MABP (mm Hg)	99.44±13.19	93.45±17.81	95.33±17.91	0.368
SBP (mm Hg)	147.91±25.90	148.47±29.21	151.38±29.41	0.877
DBP (mm Hg)	69.80±10.81	63.29±13.61	62.30±14.11	0.057
HR (bpm)	78.89±17.00	84.09±13.89	77.74±15.90	0.252

*The P value was calculated using ANOVA and χ^2 statistic tests at 95% levels of confidence intervals.
BMI, Body mass index; EF, Ejection fraction; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; MABP, Mean arterial blood pressure

Table 2. Frequencies of individuals in the different drug groups violating the protocol

Group	Additional Drugs (%)		P*
	No	Yes	
Propofol	17 (56.7)	13 (43.3)	
Etomidate	26 (86.7)	4 (13.3)	0.003
Midazolam	27 (90.0)	3 (10.0)	

*The P value was calculated using χ2 statistic tests at 95% levels of confidence intervals.

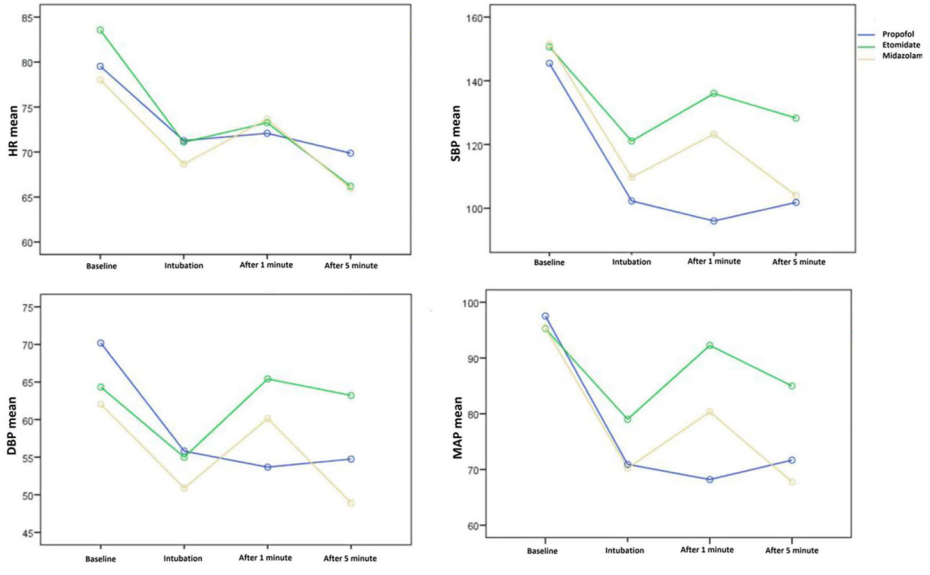

Figure 2. Intra- and inter-group comparison of HR, SBP, DBP, and MABP of the patients

Table 3. Intra- and intergroup comparisons of HR, SBP, DBP, and MABP among the 3 drug groups

Variable	Times (mean±SD)				P*
	Baseline	Intubation	After 1 min	After 5 min	
HR (bpm)					0.065
Propofol	78.89±17.00	71.00±14.01	70.81±15.29	68.28±15.41	
Etomidate	84.09±13.89	71.33±13.81	74.39±14.69	67.59±10.52	
Midazolam	87.1±16.1	68.92±12.54	73.81±16.2	66.11±15.20	
P*					0.688
SBP (mm Hg)					<0.001
Propofol	147.91±25.90	105.04±24.91	99.11±20.52	103.49±2139	
Etomidate	148.47±29.21	118.73±25.01	133.22±39.01	126.81±27.00	
Midazolam	151.22±29.89	109.41±24.42	122.92±24.36	103.81±18.74	
P*					<0.001
DBP (mm Hg)					<0.001
Propofol	69.81±10.81	56.46±17.80	54.71±13.91	55.42±13.89	
Etomidate	63.29±13.62	54.42±12.31	64.49±17.00	62.71±14.70	
Midazolam	61.90±14.17	50.81±12.60	60.01±14.77	48.91±11.20	
P**					0.056
MABP (mm Hg)					<0.001
Propofol	99.41±13.21	72.56±19.00	70.53±16.22	73.04±16.78	
Etomidate	93.46±17.80	77.51±15.19	90.22±26.19	83.79±17.50	
Midazolam	95.22±18.19	70.08±13.91	80.11±16.68	67.68±13.51	
P**					<0.001

*Intergroup, multivariate analysis of the repeated measures test
**Intragroup, analysis of the variances test
SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; MABP, Mean arterial blood pressure

Table 4. Intragroup mean comparisons of HR, SBP, DBP, and MABP with the baseline across the study groups

Variable	Time (mean difference ± SD)					
	Intubation	P	After 1 min	P	After 5 min	P
HR (bpm)						
Propofol	7.89±11.90	0.001	8.18±12.38	0.001	10.59±13.90	<0.001
Etomidate	12.81±9.88	<0.001	9.68±11.67	<0.001	16.49±14.09	<0.001
Midazolam	9.10±11.52	<0.001	4.22±18.10	0.209	11.49±16.09	0.001
SBP (mm Hg)						
Propofol	42.89±34.30	<0.001	48.67±37.70	<0.001	44.29±36.48	<0.001
Etomidate	29.81±23.22	<0.001	15.31±26.71	0.004	21.71±28.67	0.517
Midazolam	39.61±30.52	<0.001	27.90±33.81	<0.001	47.02±33.29	<0.001
DBP (mm Hg)						
Propofol	13.31±16.00	<0.001	15.00±15.11	<0.001	14.41±14.29	<0.001
Etomidate	9.01±9.21	<0.001	-1.13±14.50	0.672	0.66±14.31	0.801
Midazolam	10.81±15.28	<0.001	2.21±18.63	0.517	13.39±14.88	<0.001
MABP (mm Hg)						
Propofol	26.67±20.51	<0.001	29.90±20.29	<0.001	26.51±20.89	<0.001
Etomidate	16.00±16.41	<0.001	3.28±21.10	0.394	9.67±19.49	0.001
Midazolam	24.29±18.67	<0.001	15.22±23.22	0.001	27.67±19.89	<0.001

The P value was calculated using the paired t test compared with the baseline time.
SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; MABP, Mean arterial blood pressure

Discussion

Maintaining hemodynamic stability in patients undergoing CABG during anesthesia and the surgical procedure is of paramount importance. Each anesthetic agent elicits specific hemodynamic changes, necessitating the selection of an anesthetic regimen that optimally maintains the patient's physiological equilibrium.[5] The findings of this study indicate that, overall, the least extent of hemodynamic changes occurred in the etomidate group, followed by the midazolam group, while the propofol group displayed more substantial hemodynamic fluctuations and required greater vasopressor use. This is consistent with prior research, such as the study conducted by Kaushal et al[19] (2015), demonstrating that etomidate provided more stable hemodynamic parameters than propofol in patients undergoing CABG and mitral valvuloplasty.

Aggarwal et al[12] (2015), comparing propofol and etomidate

in patients undergoing general anesthesia, observed that the etomidate group exhibited minor changes in MABP and HR compared with the baseline, in contrast to the propofol group. Similarly, a clinical trial by Masoudifar et al[20] (2013), evaluating cardiovascular responses to laryngoscopy and intubation following induction with propofol and etomidate, found that propofol induced greater variations in SBP, DBP, and MABP, though no differences were noted in HR and oxygen saturation. This finding led to the conclusion that etomidate offered superior hemodynamic stability compared with propofol.

Although the significance of hemodynamic changes resulting from administered drugs may vary in different studies, the aforementioned studies align with the findings of the current research regarding etomidate and propofol groups.

In this study, all 3 groups exhibited a decrease in SBP, DBP, MABP, and HR after induction, with the propofol group displaying the most pronounced hemodynamic alterations. The observed decrease in blood pressure following propofol induction can likely be explained by the drug's vasodilatory properties. Propofol inhibits the sympathetic nervous system and reduces systemic vascular resistance, which in turn decreases blood pressure. Additionally, propofol may also affect cardiac output and cardiac sympathetic nerves, further contributing to its impact on hemodynamics during anesthesia induction.[21] Midazolam, on the other hand, diminishes vascular sympathetic tone by affecting the vasomotor center in the brainstem, leading to peripheral vasodilation and decreased blood pressure.[22] Etomidate's blood pressure-lowering effect can be attributed to its interaction with GABA receptors, which leads to reduced sympathetic nervous system activity by enhancing baroreceptor activity. This interaction results in minimal cardiovascular changes. The absence of histamine release during etomidate induction also contributes to the observable decrease in blood pressure.[19]

Soleimani et al[18] (2017) compared the effects of diazepam, propofol, and etomidate during anesthesia induction in patients undergoing CABG and found a decrease from the baseline in SBP, DBP, and MAP in all 3 groups. Nonetheless, these variables were lower in the diazepam group than in the other groups.

In the present study, the etomidate group demonstrated the least extent of change in SBP and MABP, followed by the midazolam group. For HR, the least change was observed in the midazolam group, followed by the propofol group.

The current study's unique aspects include differences in the dosage of propofol administered, the surgical context, and the relevance of HR variations.

Post intubation, the values of HR, SBP, DBP, and MABP increased in the etomidate and midazolam groups at 1 and 5 minutes, possibly due to pain and sympathetic stimulation triggered by the intubation process. In contrast, the propofol group displayed HR elevation only. Remarkably, 30% of the propofol group exhibited a decrease in blood pressure following intubation, which did not recover even after the vasopressor administration, emphasizing the clinical significance of this finding.

The limitations of this study include small sample size, the occurrence of severe hemodynamic complications during anesthesia, data collection confined to a single center, an absence of depth-of-anesthesia monitoring, and a lack of measurements for drug levels in the blood.

Conclusion

The present study, along with other research findings, suggests that etomidate, followed by midazolam, serves as a suitable option for maintaining stable hemodynamic parameters during anesthesia, while propofol demonstrates lower stability. It is important to note that the limitations of this study include the inability to measure blood levels of the anesthetic agents, which makes it difficult to ascertain whether the observed outcomes occurred at the same drug concentrations. Future studies can incorporate blood level measurements of the drugs to enhance the precision of their findings. Despite numerous Iranian and international studies investigating the effects of various anesthetic agents on hemodynamic parameters, a consensus has yet to be reached, indicating the need for further research in this area to provide more conclusive evidence and guide clinical practice effectively.

Acknowledgments

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