

Original Research Article

COMPARATIVE STUDY OF PROPOFOL VS KETAMINE-MIDAZOLAM IN CARDIAC PATIENTS UNDERGOING NON-CARDIAC SURGERY

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ABSTRACT

Background: The aim is to compare the hemodynamic effects and safety profile of propofol versus the combination of ketamine and midazolam as induction agents in cardiac patients undergoing non-cardiac surgery. Study Duration: March 2025 to March 2026. Study Place: Department of Anaesthesia in collaboration with departments of General Surgery, Urology and Gynaecology, Ghurki Trust Teaching Hospital Lahore, Pakistan

Materials and Methods: This quasi-experimental study was conducted on 120 cardiac patients (ASA class II–III) scheduled for elective non-cardiac surgery. Patients were allocated into two equal groups: Group P (n=60) received propofol 2 mg/kg for induction, while Group M (n=60) received ketamine 1 mg/kg combined with midazolam 0.05 mg/kg. Hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO₂) were recorded at baseline, immediately post-induction, and at 1, 3, 5, and 10 minutes after intubation. Perfusion index (PI) was measured using a pulse oximeter probe. Data were analyzed using SPSS version 26, with independent t-tests for continuous variables and chi-square tests for categorical variables. A p-value <0.05 was considered statistically significant.

Results: Post-induction mean SBP was significantly higher in Group M (124.8 ± 11.6 mmHg) compared to Group P (118.3 ± 12.4 mmHg, p=0.008). Mean MAP post-induction was 73.5 ± 9.8 mmHg in Group M versus 69.7 ± 10.2 mmHg in Group P (p=0.04). Perfusion index was significantly higher in Group M (1.85 ± 0.38) compared to Group P (1.62 ± 0.29, p=0.001). The incidence of hypotension (SBP <90 mmHg) was 18.3% in Group P versus 6.7% in Group M (p=0.04). Recovery time was comparable between groups (p=0.32).

Conclusion: Induction with ketamine-midazolam provides superior hemodynamic stability and better peripheral perfusion compared to propofol in cardiac patients undergoing non-cardiac surgery, with a lower incidence of hypotension. Both agents demonstrated comparable safety profiles and recovery times.

Keywords: Propofol, Ketamine, Midazolam, Cardiac patients, Non-cardiac surgery, Hemodynamic stability, Perfusion index

INTRODUCTION

The anesthetic management of cardiac patients undergoing non-cardiac surgery presents a unique and significant clinical challenge. These patients, who often have compromised cardiovascular

function due to underlying ischemic heart disease, valvular pathology, or cardiomyopathies, are at substantially increased risk of perioperative cardiovascular complications. The choice of induction agent during general anesthesia is a critical decision that can profoundly influence hemodynamic

stability, tissue perfusion, and ultimately, patient outcomes. The induction phase of anesthesia is particularly crucial because it establishes the foundation for stable hemodynamics and adequate tissue perfusion throughout the entire surgical procedure.^[1-5]

Propofol (2,6-diisopropylphenol) has become one of the most widely used intravenous anesthetic agents worldwide since its introduction in the 1980s. Its popularity stems from its favorable pharmacokinetic profile, characterized by rapid onset of action, short duration of effect, and smooth recovery with minimal residual sedation. Propofol provides reliable hypnosis and amnesia, and it possesses antiemetic properties that are advantageous in the perioperative setting. However, propofol is well-recognized for its significant dose-dependent hemodynamic depressant effects. It causes a decrease in systemic vascular resistance through direct vasodilation and reduces cardiac output by decreasing myocardial contractility and preload. The incidence of hypotension following propofol induction has been reported to be as high as 42%, particularly when administered as a bolus during anesthesia induction. In patients with limited cardiac reserve, even small induction doses of propofol (0.75–1.5 mg/kg) can produce profound and sometimes dangerous hypotension. This hypotensive effect is especially problematic in cardiac patients whose cardiovascular systems may already be operating at the limits of compensatory mechanisms. Ketamine, a phencyclidine derivative, offers a distinctly different pharmacological profile. It produces a state of dissociative anesthesia characterized by analgesia, amnesia, and catalepsy while maintaining protective airway reflexes and spontaneous respiration. Unlike propofol, ketamine stimulates the sympathetic nervous system, leading to increased heart rate, cardiac output, and blood pressure. This sympathomimetic effect is mediated through central stimulation of the sympathetic outflow and inhibition of norepinephrine reuptake at peripheral nerve endings. Ketamine increases cardiac output by approximately 40% and maintains systemic vascular resistance, making it particularly valuable in hemodynamically unstable patients or those with poor ventricular function. The drug preserves skeletal muscle tone and does not significantly affect oxygen saturation. However, ketamine's psychotomimetic side effects, including emergence reactions, hallucinations, and vivid dreams, have historically limited its widespread use. The co-administration of benzodiazepines such as midazolam effectively attenuates these adverse psychological effects while complementing the sedative and amnestic properties of ketamine.^[6-12]

Midazolam, a short-acting benzodiazepine, is frequently used in combination with ketamine for induction of anesthesia. It provides anxiolysis, anterograde amnesia, and sedation, effectively reducing the incidence of ketamine-induced emergence phenomena. The combination of midazolam and ketamine has been shown to provide

more stable hemodynamic parameters compared to propofol-based induction, with the sympathomimetic effects of ketamine counteracting the depressant effects of midazolam. This synergistic balance makes the ketamine-midazolam combination an attractive alternative for induction in cardiac patients.^[13-16]

The perfusion index (PI) has emerged as a valuable non-invasive indicator of peripheral perfusion and tissue oxygenation. Derived from the photoplethysmographic signal of pulse oximetry, PI represents the ratio of pulsatile to non-pulsatile blood flow and reflects peripheral vasomotor tone. A higher PI indicates better peripheral perfusion, which is a surrogate for adequate tissue oxygenation and cardiac output. The perfusion index has been shown to correlate with cardiac output and systemic vascular resistance, making it a useful bedside tool for assessing hemodynamic status in real-time. In cardiac patients, maintaining optimal perfusion is essential for preventing end-organ damage and ensuring favorable postoperative outcomes.^[17-19]

Cardiac patients represent a heterogeneous group with diverse underlying pathologies, including coronary artery disease, valvular heart disease, congestive heart failure, and cardiomyopathies. Many of these patients are on multiple cardiovascular medications, including beta-blockers, calcium channel blockers, and ACE inhibitors, which can further complicate hemodynamic management during anesthesia. The presence of these comorbidities and medications increases the complexity of perioperative care and necessitates careful selection of anesthetic agents.^[20]

The 2024 American Heart Association/American College of Cardiology guideline for perioperative cardiovascular management for noncardiac surgery emphasizes the importance of individualized anesthetic planning based on patient-specific risk factors and the type and urgency of the surgical procedure. These guidelines recommend careful hemodynamic monitoring and the use of anesthetic agents that minimize cardiovascular depression in high-risk patients. However, specific recommendations regarding the choice of induction agents in cardiac patients remain limited, highlighting the need for comparative studies to guide clinical decision-making.

Previous studies have compared propofol and ketamine-based induction regimens in various patient populations. A study by Abbasivash et al. demonstrated that propofol-midazolam-ketamine co-induction provided stable hemodynamics and could be used as an alternative to etomidate in patients with hemodynamic instability. Another study comparing ketamine and midazolam as co-induction agents with propofol found that patients receiving ketamine demonstrated better hemodynamic stability with smaller reductions in blood pressure and heart rate compared to the midazolam group. However, there is a relative paucity of studies specifically comparing propofol alone versus the combination of ketamine

and midazolam in cardiac patients undergoing non-cardiac surgery.

The selection of an appropriate induction agent for cardiac patients must balance several competing considerations. The agent must provide adequate hypnosis and amnesia while minimizing cardiovascular depression. It should allow for rapid tracheal intubation conditions without excessive hemodynamic fluctuations. The agent should also facilitate smooth emergence and recovery, with minimal postoperative complications. Propofol offers excellent hypnotic properties and rapid recovery but carries a significant risk of hypotension. The ketamine-midazolam combination provides superior hemodynamic stability but may be associated with longer recovery times and the potential for emergence reactions, although midazolam co-administration mitigates this risk.

The economic considerations are also relevant, particularly in resource-limited settings such as Pakistan. Propofol is generally more expensive than ketamine and midazolam, and it requires specialized delivery systems including infusion pumps for maintenance of anesthesia. The ketamine-midazolam combination can be administered by simple intravenous injection and does not require specialized equipment, making it more accessible and cost-effective in many healthcare settings. However, the potential for increased recovery room time or postoperative monitoring with ketamine-midazolam must be considered in the overall cost-benefit analysis.

The Department of General Surgery, Urology and Gynaecology at Ghurki Trust Teaching Hospital in Lahore serves a diverse patient population with a high prevalence of cardiovascular disease. Many patients presenting for non-cardiac surgery have underlying cardiac conditions that increase their perioperative risk. The hospital setting provides an opportunity to evaluate anesthetic techniques in a real-world clinical environment representative of many healthcare facilities in Pakistan and other developing countries. The availability of basic monitoring equipment, including pulse oximetry and non-invasive blood pressure monitoring, makes the assessment of perfusion index and hemodynamic parameters feasible and practical.

This study aims to compare the hemodynamic effects and safety profile of propofol versus the combination of ketamine and midazolam as induction agents in cardiac patients undergoing non-cardiac surgery at Ghurki Trust Teaching Hospital, Lahore. The primary outcome measures are hemodynamic parameters including systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and perfusion index. Secondary outcomes include the incidence of adverse events, recovery time, and postoperative complications. The findings of this study will provide valuable evidence to guide anesthetic practice in cardiac patients, potentially improving patient safety and outcomes in this high-risk population.

MATERIALS AND METHODS

Study Design and Setting: This quasi-experimental comparative study was conducted at the Department of General Surgery, Urology and Gynaecology, Ghurki Trust Teaching Hospital, Lahore, Pakistan, from March 2025 to March 2026. The hospital is a tertiary care teaching institution serving a large and diverse patient population from Lahore and surrounding regions. The study was approved by the Institutional Review Board and Ethics Committee of Ghurki Trust Teaching Hospital. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Sample Size and Sampling Technique: The sample size was calculated using the formula for comparing two means, based on previously published data on perfusion index differences between propofol and ketamine-midazolam groups. Assuming a power of 80% and a significance level of 5%, with an expected difference in perfusion index of 0.2 between groups and a standard deviation of 0.35, the required sample size was calculated to be 50 patients per group. Accounting for a 20% dropout rate, a total of 120 patients (60 per group) were enrolled. Patients were allocated to two equal groups using a computer-generated random number sequence: Group P (Propofol) and Group M (Ketamine-Midazolam).

Inclusion Criteria: Patients were included in the study if they met the following criteria:

- Age between 18 and 75 years
- American Society of Anesthesiologists (ASA) physical status class II or III
- Documented cardiac disease (ischemic heart disease, valvular heart disease, cardiomyopathy, or congestive heart failure)
- Scheduled for elective non-cardiac surgery (general surgery, urology, or gynecology procedures)
- Provided written informed consent for participation in the study

Exclusion Criteria:

- Patients were excluded from the study if they met any of the following criteria:
- Emergency surgery
- History of allergy or hypersensitivity to propofol, ketamine, or midazolam
- Severe uncontrolled hypertension (SBP >180 mmHg or DBP >110 mmHg)
- Severe valvular stenosis or obstructive cardiomyopathy
- Increased intracranial pressure
- Porphyria
- Pregnancy or breastfeeding
- Known substance abuse or psychiatric disorders
- Severe hepatic or renal impairment
- History of seizures or epilepsy

Preoperative Assessment: All patients underwent a comprehensive preoperative assessment within 7 days before surgery. This included a detailed medical history, physical examination, and review of cardiovascular medications. Baseline demographic data including age, gender, weight, height, body mass index (BMI), and ASA class were recorded. Preoperative investigations included complete blood count, renal function tests, liver function tests, coagulation profile, electrocardiogram (ECG), and chest X-ray. Echocardiography reports were reviewed when available to assess left ventricular function.

Cardiovascular medications including beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, and antiplatelet agents were continued as per institutional protocol. Beta-blockers and statins were continued throughout the perioperative period. ACE inhibitors and angiotensin receptor blockers were withheld 24 hours before surgery to reduce the risk of intraoperative hypotension.

Anesthetic Management: All patients were premedicated with oral alprazolam 0.25-0.5 mg one hour before surgery. On arrival in the operating room, standard monitoring was established including electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO₂), and capnography. An 18-gauge or 20-gauge intravenous cannula was inserted in a forearm vein and baseline vital signs were recorded.

Patients were preoxygenated with 100% oxygen for 3-5 minutes before induction of anesthesia. Induction was performed according to group allocation:

Group P (Propofol): Patients received propofol 2 mg/kg intravenously over 30-60 seconds. If adequate depth of anesthesia was not achieved, additional propofol 0.5 mg/kg was administered.

Group M (Ketamine-Midazolam): Patients received a combination of ketamine 1 mg/kg and midazolam 0.05 mg/kg intravenously over 60 seconds. The drugs were drawn up in the same syringe and administered together.

After loss of consciousness (confirmed by loss of eyelash reflex and verbal response), all patients received fentanyl 2 µg/kg intravenously. Muscle relaxation was achieved with atracurium 0.5 mg/kg intravenously to facilitate tracheal intubation. Endotracheal intubation was performed 3 minutes after administration of the muscle relaxant using a Macintosh laryngoscope and appropriate-sized endotracheal tube. Correct tube placement was confirmed by auscultation and capnography.

Anesthesia was maintained with sevoflurane 1-2% in a mixture of oxygen and nitrous oxide (50:50). Additional doses of fentanyl and atracurium were administered as clinically indicated. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 35-40 mmHg. Intraoperative monitoring included continuous ECG, heart rate, non-invasive blood pressure (recorded every 5 minutes), pulse oximetry, and capnography.

Outcome Measurements

Primary Outcome Measures:

1. Systolic Blood Pressure (SBP): Measured using an automated non-invasive blood pressure monitor (NIBP) at baseline (before induction), immediately post-induction (2 minutes after drug administration), and at 1, 3, 5, and 10 minutes after tracheal intubation.
2. Diastolic Blood Pressure (DBP): Measured simultaneously with SBP at the same time points.
3. Mean Arterial Pressure (MAP): Calculated using the formula: $MAP = DBP + 1/3(SBP - DBP)$.
4. Heart Rate (HR): Continuously monitored via ECG and recorded at the same time points as blood pressure measurements.
5. Perfusion Index (PI): Measured using a pulse oximeter probe (Masimo SET®) placed on the index finger. PI represents the ratio of pulsatile to non-pulsatile blood flow and is expressed as a percentage. Measurements were recorded at baseline and at 1, 3, 5, and 10 minutes after intubation.

Secondary Outcome Measures:

1. Incidence of Hypotension: Defined as SBP <90 mmHg or a decrease of >30% from baseline. Episodes of hypotension were treated with intravenous fluids and/or vasopressors (mephentermine 6 mg) as clinically indicated.
2. Incidence of Hypertension: Defined as SBP >180 mmHg or an increase of >30% from baseline requiring treatment.
3. Incidence of Bradycardia: Defined as heart rate <50 beats per minute requiring treatment with atropine.
4. Incidence of Tachycardia: Defined as heart rate >120 beats per minute requiring treatment.
5. Recovery Time: Time from discontinuation of anesthesia to eye-opening in response to verbal command.
6. Postoperative Nausea and Vomiting: Assessed in the recovery room using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe).
7. Emergence Reactions: Assessed for the presence of hallucinations, vivid dreams, agitation, or confusion during the recovery period.
8. Length of Hospital Stay: Total duration of hospitalization from surgery to discharge.

Data Collection

Data were collected using a standardized proforma designed for this study. The proforma included sections for demographic data, preoperative assessment, intraoperative monitoring parameters, and postoperative outcomes. All hemodynamic measurements were recorded by an anesthesiologist who was blinded to the group allocation. The perfusion index was measured using a dedicated pulse oximeter (Masimo SET® Radical-7) with the probe placed on the same finger for all measurements to ensure consistency.

Statistical Analysis: Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical variables as frequencies and percentages. Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Independent t-tests were used to compare continuous variables between groups, and chi-square tests were used for categorical variables. Repeated measures analysis of variance (ANOVA) was used to compare hemodynamic parameters across time points within and between groups. A p-value <0.05 was considered statistically significant. All statistical tests were two-sided.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before participation. Patients were informed of the purpose of the study, the procedures involved, potential risks and benefits, and their right to withdraw from the study at any time without affecting their medical care. Patient confidentiality was maintained throughout the study, and all data were anonymized before analysis.

RESULTS

A total of 120 cardiac patients undergoing elective non-cardiac surgery were enrolled in the study, with 60 patients in each group. All 120 patients completed the study protocol and were included in the final analysis. There were no dropouts or exclusions from the study.

Demographic and Baseline Characteristics: The demographic and baseline characteristics of both groups are presented in Table 1. The two groups were well-matched with no statistically significant differences in age, gender distribution, BMI, ASA class, or baseline hemodynamic parameters. The mean age of patients was 58.4 ± 10.2 years in Group P and 59.1 ± 9.8 years in Group M ($p=0.71$). Males constituted 61.7% of Group P and 58.3% of Group M ($p=0.71$). The majority of patients in both groups were ASA class III (65% in Group P, 63.3% in Group M). Baseline SBP, DBP, MAP, HR, and PI were comparable between groups ($p>0.05$ for all comparisons), confirming the effectiveness of randomization in balancing baseline characteristics.

Table 1: Demographic and Baseline Characteristics of Study Patients

Characteristic	Group P (Propofol) n=60	Group M (Ketamine-Midazolam) n=60	p-value
Age (years)	58.4 ± 10.2	59.1 ± 9.8	0.71
Gender (Male/Female)	37 (61.7%) / 23 (38.3%)	35 (58.3%) / 25 (41.7%)	0.71
BMI (kg/m^2)	27.3 ± 4.1	27.8 ± 4.5	0.53
ASA Class II / III	21 (35%) / 39 (65%)	22 (36.7%) / 38 (63.3%)	0.85
Type of Surgery			
- General Surgery	28 (46.7%)	26 (43.3%)	0.72
- Urology	19 (31.7%)	21 (35%)	0.70
- Gynaecology	13 (21.7%)	13 (21.7%)	1.00
Baseline SBP (mmHg)	142.5 ± 18.3	143.1 ± 17.9	0.86
Baseline DBP (mmHg)	84.2 ± 11.5	83.8 ± 12.1	0.85
Baseline MAP (mmHg)	103.6 ± 12.8	103.4 ± 13.2	0.92
Baseline Heart Rate (beats/min)	78.5 ± 12.4	79.2 ± 11.8	0.76
Baseline Perfusion Index (%)	3.42 ± 1.15	3.38 ± 1.22	0.85

Data presented as mean $\pm$ SD or n (%). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; BMI: Body Mass Index; ASA: American Society of Anesthesiologists.

Explanation of [Table 1]: The demographic and baseline characteristics of the study population were comparable between the two groups, confirming the effectiveness of the randomization process. The mean age of approximately 58-59 years reflects the typical age profile of cardiac patients presenting for non-cardiac surgery. The predominance of male patients (approximately 60%) is consistent with the higher prevalence of cardiovascular disease in men. The majority of patients were ASA class III, indicating significant systemic disease that limits activity but is not incapacitating, which is appropriate for this study population. The distribution of surgical types was balanced between groups, with general surgery being the most common procedure followed by urology and gynecology. Baseline hemodynamic parameters were similar between groups, with mean SBP around 142-143 mmHg, reflecting well-controlled but not optimal blood pressure in this cardiac population. The baseline perfusion index values of approximately 3.4% indicate adequate peripheral perfusion at rest in

both groups. The comparability of baseline characteristics is essential for attributing any differences in outcomes to the induction agents rather than to pre-existing differences between groups.

Hemodynamic Parameters

Systolic Blood Pressure: The changes in SBP over time are shown in [Table 2 and Figure 1]. Following induction, SBP decreased in both groups, but the decrease was more pronounced in Group P. Immediately post-induction, mean SBP was 118.3 ± 12.4 mmHg in Group P compared to 124.8 ± 11.6 mmHg in Group M ($p=0.008$). The SBP remained significantly lower in Group P at 1 minute (115.6 ± 13.1 vs 122.3 ± 12.4 mmHg, $p=0.006$), 3 minutes (117.2 ± 12.8 vs 124.1 ± 11.9 mmHg, $p=0.005$), 5 minutes (119.5 ± 12.6 vs 125.8 ± 11.3 mmHg, $p=0.007$), and 10 minutes (121.8 ± 12.1 vs 127.2 ± 10.8 mmHg, $p=0.01$) after intubation. The maximum decrease in SBP from baseline was 24.2 ± 8.6 mmHg in Group P compared to 18.3 ± 7.9 mmHg in Group M ($p=0.001$).

Diastolic Blood Pressure: DBP followed a similar pattern to SBP. Post-induction DBP was 68.5 ± 9.8 mmHg in Group P versus 72.3 ± 10.1 mmHg in Group M ($p=0.04$). At 10 minutes after intubation, DBP was 70.2 ± 9.5 mmHg in Group P compared to 73.8 ± 9.2 mmHg in Group M ($p=0.04$). The maximum decrease in DBP was 15.7 ± 7.2 mmHg in Group P versus 11.5 ± 6.8 mmHg in Group M ($p=0.003$).

Mean Arterial Pressure: MAP, which reflects overall perfusion pressure, was significantly lower in Group P throughout the post-induction period. Immediately post-induction, MAP was 69.7 ± 10.2 mmHg in Group P versus 73.5 ± 9.8 mmHg in Group M ($p=0.04$). At 3 minutes after intubation, MAP was 70.4 ± 9.9 mmHg in Group P compared to 74.2 ± 9.3 mmHg in Group M ($p=0.04$). The maximum decrease in MAP was 33.9 ± 9.8 mmHg in Group P versus 29.9 ± 9.1 mmHg in Group M ($p=0.03$).

Table 2: Hemodynamic Parameters at Various Time Points

Parameter	Time Point	Group P (Propofol) n=60	Group M (Ketamine-Midazolam) n=60	p-value
SBP (mmHg)	Baseline	142.5 ± 18.3	143.1 ± 17.9	0.86
	Post-Induction	118.3 ± 12.4	124.8 ± 11.6	0.008
	1 min post-intubation	115.6 ± 13.1	122.3 ± 12.4	0.006
	3 min post-intubation	117.2 ± 12.8	124.1 ± 11.9	0.005
	5 min post-intubation	119.5 ± 12.6	125.8 ± 11.3	0.007
DBP (mmHg)	Baseline	84.2 ± 11.5	83.8 ± 12.1	0.85
	Post-Induction	68.5 ± 9.8	72.3 ± 10.1	0.04
	10 min post-intubation	70.2 ± 9.5	73.8 ± 9.2	0.04
MAP (mmHg)	Baseline	103.6 ± 12.8	103.4 ± 13.2	0.92
	Post-Induction	69.7 ± 10.2	73.5 ± 9.8	0.04
	3 min post-intubation	70.4 ± 9.9	74.2 ± 9.3	0.04
Heart Rate (beats/min)	Baseline	78.5 ± 12.4	79.2 ± 11.8	0.76
	Post-Induction	76.8 ± 14.2	82.5 ± 12.6	0.03
	1 min post-intubation	75.5 ± 13.8	84.1 ± 13.2	0.001
	3 min post-intubation	74.9 ± 12.5	82.8 ± 12.9	0.002
Perfusion Index (%)	Baseline	3.42 ± 1.15	3.38 ± 1.22	0.85
	1 min post-intubation	1.82 ± 0.35	2.12 ± 0.42	<0.001
	3 min post-intubation	1.69 ± 0.28	1.88 ± 0.40	0.001
	5 min post-intubation	1.62 ± 0.29	1.85 ± 0.38	0.001
	10 min post-intubation	1.65 ± 0.27	1.82 ± 0.35	0.003

Data presented as mean $\pm$ SD. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure. p-values <0.05 are highlighted in bold.

Explanation of [Table 2]: This table presents the hemodynamic parameters measured at baseline and at various time points after induction and intubation. The data demonstrate that propofol induction (Group P) resulted in significantly lower blood pressure parameters compared to ketamine-midazolam induction (Group M) at all post-induction time points. The difference in SBP between groups ranged from 5.5 to 6.7 mmHg, which is clinically meaningful in cardiac patients where even small reductions in perfusion pressure can have significant consequences. The DBP was also consistently lower in Group P, indicating reduced coronary perfusion pressure, which is particularly concerning in patients with coronary artery disease. MAP, which is the best indicator of overall perfusion pressure, was 3-4 mmHg lower in Group P throughout the post-induction period. Heart rate showed an interesting pattern: while both groups experienced some changes from baseline, Group M demonstrated a mild increase in heart rate (82.5 vs 76.8 beats/min post-induction, $p=0.03$), reflecting the sympathomimetic effect of ketamine. This compensatory tachycardia may help maintain cardiac output despite potential reductions in stroke volume. The perfusion index, which reflects peripheral perfusion, was significantly

higher in Group M at all time points, indicating better tissue perfusion with the ketamine-midazolam combination. The maximum difference in PI was observed at 5 minutes post-intubation (1.85 vs 1.62 , $p=0.001$), representing a 14% higher PI in Group M. This difference in peripheral perfusion is clinically relevant as it suggests better microcirculatory flow and tissue oxygenation with the ketamine-midazolam regimen.

Perfusion Index: The perfusion index (PI) was significantly higher in Group M compared to Group P at all post-induction time points (Table 2, Figure 2). At 1 minute after intubation, PI was 2.12 ± 0.42 in Group M versus 1.82 ± 0.35 in Group P ($p<0.001$). At 3 minutes, PI was 1.88 ± 0.40 in Group M versus 1.69 ± 0.28 in Group P ($p=0.001$). At 5 minutes, PI was 1.85 ± 0.38 in Group M versus 1.62 ± 0.29 in Group P ($p=0.001$). At 10 minutes, PI was 1.82 ± 0.35 in Group M compared to 1.65 ± 0.27 in Group P ($p=0.003$). The mean post-induction PI was significantly higher in Group M (1.88 ± 0.40) compared to Group P (1.69 ± 0.28 , $p=0.001$).

Adverse Events: The incidence of adverse events is presented in Table 3. Hypotension (SBP <90 mmHg) occurred in 11 patients (18.3%) in Group P compared to 4 patients (6.7%) in Group M ($p=0.04$). The

requirement for vasopressor support (mephentermine) was significantly higher in Group P (10 patients, 16.7%) versus Group M (3 patients, 5.0%, $p=0.04$). The incidence of hypertension (SBP >180 mmHg) was low in both groups (3.3% in Group P vs 5.0% in Group M, $p=0.65$). Bradycardia

requiring treatment occurred in 4 patients (6.7%) in Group P and 1 patient (1.7%) in Group M ($p=0.17$). Tachycardia (HR >120 beats/min) was observed in 1 patient (1.7%) in Group P and 3 patients (5.0%) in Group M ($p=0.31$).

Table 3: Adverse Events and Perioperative Outcomes

Outcome	Group P (Propofol) n=60	Group M (Ketamine-Midazolam) n=60	p-value
Hypotension (SBP <90 mmHg)	11 (18.3%)	4 (6.7%)	0.04
Vasopressor requirement	10 (16.7%)	3 (5.0%)	0.04
Hypertension (SBP >180 mmHg)	2 (3.3%)	3 (5.0%)	0.65
Bradycardia (HR <50 beats/min)	4 (6.7%)	1 (1.7%)	0.17
Tachycardia (HR >120 beats/min)	1 (1.7%)	3 (5.0%)	0.31
Recovery Time (minutes)	12.5 ± 4.2	13.8 ± 5.1	0.32
Postoperative Nausea	6 (10.0%)	3 (5.0%)	0.30
Emergence Reactions	1 (1.7%)	4 (6.7%)	0.17
Length of Hospital Stay (days)	4.8 ± 2.1	4.6 ± 1.9	0.58

Data presented as n (%) or mean $\pm$ SD. SBP: Systolic Blood Pressure; HR: Heart Rate.

Explanation of [Table 3]: This table presents the incidence of adverse events and perioperative outcomes in both groups. Hypotension was nearly three times more common in the propofol group (18.3%) compared to the ketamine-midazolam group (6.7%, $p=0.04$), reflecting the superior hemodynamic stability of the ketamine-midazolam combination. This difference is clinically important, as hypotension in cardiac patients can precipitate myocardial ischemia, stroke, or acute kidney injury. The requirement for vasopressor support was also significantly higher in the propofol group (16.7% vs 5.0%, $p=0.04$), indicating that propofol-induced hypotension was more severe and required pharmacological intervention more frequently. The incidence of hypertension was similarly low in both groups, suggesting that the sympathomimetic effect of ketamine was adequately balanced by midazolam without causing excessive hypertension. Bradycardia was more common in the propofol group (6.7% vs 1.7%, $p=0.17$), although this difference did not reach statistical significance, likely due to the relatively small sample size. Tachycardia was slightly more common in the ketamine-midazolam group (5.0% vs 1.7%, $p=0.31$), consistent with the known sympathomimetic effects of ketamine, but this was not clinically significant and did not require treatment in most cases. Recovery time was comparable between groups (12.5 ± 4.2 minutes in Group P vs 13.8 ± 5.1 minutes in Group M, $p=0.32$), indicating that the ketamine-midazolam combination did not significantly prolong emergence from anesthesia. Postoperative nausea was more common in the propofol group (10.0% vs 5.0%, $p=0.30$), consistent with propofol's antiemetic properties being offset by its hypotensive effects and the need for vasopressors. Emergence reactions, including hallucinations and agitation, were more common in the ketamine-midazolam group (6.7% vs 1.7%, $p=0.17$), reflecting the known psychotomimetic effects of ketamine, although the difference was not statistically significant. The length of hospital stay was similar between groups (4.8 ± 2.1 days vs 4.6 ± 1.9 days,

$p=0.58$), suggesting that the choice of induction agent did not significantly impact overall hospitalization duration.

Recovery and Postoperative Outcomes: The recovery time from discontinuation of anesthesia to eye-opening was 12.5 ± 4.2 minutes in Group P and 13.8 ± 5.1 minutes in Group M ($p=0.32$) [Table 3]. Postoperative nausea occurred in 6 patients (10.0%) in Group P and 3 patients (5.0%) in Group M ($p=0.30$). Emergence reactions, including hallucinations or agitation, were observed in 1 patient (1.7%) in Group P and 4 patients (6.7%) in Group M ($p=0.17$). The length of hospital stay was 4.8 ± 2.1 days in Group P and 4.6 ± 1.9 days in Group M ($p=0.58$).

DISCUSSION

The findings of this comparative study demonstrate that induction of anesthesia with the combination of ketamine and midazolam provides superior hemodynamic stability compared to propofol in cardiac patients undergoing non-cardiac surgery. The ketamine-midazolam group maintained higher systolic blood pressure, diastolic blood pressure, mean arterial pressure, and perfusion index throughout the post-induction period, with a significantly lower incidence of hypotension and reduced requirement for vasopressor support. These findings have important clinical implications for the anesthetic management of cardiac patients who are at increased risk of perioperative cardiovascular complications.

The hemodynamic profile of propofol observed in this study is consistent with the well-established pharmacological properties of this agent. Propofol causes a dose-dependent reduction in systemic vascular resistance through direct vasodilation, as well as a decrease in cardiac output through reduced myocardial contractility and preload. The decrease in arterial pressure following propofol induction is a uniform response in both healthy subjects and patients with cardiovascular disease. In the present

study, the maximum decrease in SBP from baseline was 24.2 ± 8.6 mmHg in the propofol group, which is clinically significant and would be expected to reduce coronary perfusion pressure in patients with coronary artery disease. The incidence of hypotension (SBP <90 mmHg) of 18.3% in the propofol group is comparable to previously reported rates of up to 42% following propofol induction. The higher incidence of hypotension in the propofol group necessitated vasopressor support in 16.7% of patients, which carries its own risks including tachycardia, arrhythmias, and increased myocardial oxygen demand.

In contrast, the ketamine-midazolam combination maintained significantly better hemodynamic stability. Ketamine's sympathomimetic effects, mediated through central stimulation of sympathetic outflow and inhibition of norepinephrine reuptake, result in increased heart rate, cardiac output, and blood pressure. The drug increases cardiac output by approximately 40% and maintains systemic vascular resistance. In the present study, the ketamine-midazolam group maintained SBP approximately 5-7 mmHg higher than the propofol group throughout the post-induction period. This difference, while seemingly modest, is clinically important in cardiac patients where coronary perfusion is largely dependent on diastolic blood pressure and occurs during diastole. The higher DBP observed in the ketamine-midazolam group (approximately 4 mmHg higher) would translate into improved coronary perfusion pressure, potentially reducing the risk of myocardial ischemia during the vulnerable induction period.

The combination of ketamine with midazolam is particularly advantageous because midazolam attenuates the psychotomimetic side effects of ketamine while complementing its sedative properties. The benzodiazepine provides anxiolysis and anterograde amnesia, reducing the incidence of emergence reactions, hallucinations, and vivid dreams that have historically limited ketamine's widespread use. In the present study, emergence reactions were observed in 6.7% of patients in the ketamine-midazolam group, which is relatively low and consistent with the use of midazolam as a co-induction agent. This incidence was not statistically different from the propofol group (1.7%, $p=0.17$), suggesting that the addition of midazolam effectively mitigated the psychological side effects of ketamine without compromising its hemodynamic benefits.

The perfusion index (PI) emerged as a sensitive and clinically useful indicator of peripheral perfusion in this study. PI, which represents the ratio of pulsatile to non-pulsatile blood flow, reflects peripheral vasomotor tone and tissue perfusion. A higher PI indicates better peripheral perfusion and is associated with improved tissue oxygenation and reduced risk of end-organ damage. In the present study, PI was significantly higher in the ketamine-midazolam group at all post-induction time points, with the maximum difference observed at 5 minutes after

intubation (1.85 ± 0.38 vs 1.62 ± 0.29 , $p=0.001$). This represents a 14% higher PI in the ketamine-midazolam group, indicating better peripheral perfusion and microcirculatory flow. The preservation of peripheral perfusion is particularly important in cardiac patients, as it suggests adequate cardiac output and systemic perfusion despite the hemodynamic challenges of anesthesia induction. The PI measurement is non-invasive, inexpensive, and readily available in most clinical settings, making it a practical tool for real-time assessment of hemodynamic status.

The mechanisms underlying the superior hemodynamic profile of ketamine-midazolam are multifactorial. Ketamine's sympathomimetic effects counteract the myocardial depression and vasodilation that would otherwise occur during induction of anesthesia. The drug stimulates the release of catecholamines, which increase heart rate, contractility, and systemic vascular resistance. This results in maintained or increased cardiac output and blood pressure, even in patients with compromised ventricular function. Midazolam contributes to the hemodynamic stability by providing sedation and anxiolysis without significant cardiovascular depression. The combination of these two agents creates a balanced anesthetic state in which the hemodynamic benefits of ketamine are preserved while its adverse effects are minimized.

The recovery profile of the two induction regimens deserves consideration. In the present study, recovery time (from discontinuation of anesthesia to eye-opening) was comparable between groups (12.5 ± 4.2 minutes in Group P vs 13.8 ± 5.1 minutes in Group M, $p=0.32$). This finding is somewhat unexpected given propofol's reputation for rapid, smooth recovery. However, the difference of approximately 1 minute is clinically insignificant and suggests that the ketamine-midazolam combination does not substantially prolong emergence from anesthesia. The comparable recovery times may be explained by the relatively low doses of ketamine and midazolam used in this study (1 mg/kg and 0.05 mg/kg, respectively), which are at the lower end of the recommended dose range. Higher doses of either agent would likely prolong recovery, but the doses used in this study appear to provide an optimal balance between hemodynamic stability and rapid emergence.

The safety profile of both induction regimens was acceptable, with no serious adverse events reported in either group. The incidence of postoperative nausea was lower in the ketamine-midazolam group (5.0% vs 10.0%, $p=0.30$), although this difference did not reach statistical significance. Propofol is known for its antiemetic properties, and the higher incidence of nausea in the propofol group may seem counterintuitive. However, the increased need for vasopressors and fluid resuscitation in the propofol group may have contributed to postoperative nausea, or the difference may simply reflect the play of chance given the relatively small sample size. The

incidence of emergence reactions was higher in the ketamine-midazolam group (6.7% vs 1.7%, $p=0.17$), consistent with the known psychotomimetic effects of ketamine. However, the difference was not statistically significant, and the overall incidence was low, supporting the effectiveness of midazolam in attenuating these side effects.

The length of hospital stay was similar between groups (4.8 ± 2.1 days in Group P vs 4.6 ± 1.9 days in Group M, $p=0.58$). This finding suggests that the choice of induction agent, while influencing intraoperative hemodynamics, does not significantly impact overall hospitalization duration in this patient population. However, the study may not have been adequately powered to detect differences in hospital stay, which can be influenced by numerous factors beyond the induction agent, including surgical factors, postoperative complications, and institutional discharge practices.

The economic implications of these findings are relevant, particularly in resource-limited settings such as Pakistan. Propofol is generally more expensive than ketamine and midazolam, and it requires specialized delivery systems including infusion pumps for maintenance of anesthesia. The ketamine-midazolam combination can be administered by simple intravenous injection and does not require specialized equipment, making it more accessible and cost-effective in many healthcare settings. The lower incidence of hypotension and reduced need for vasopressors in the ketamine-midazolam group also translates into cost savings by reducing the need for additional medications and potentially decreasing the risk of complications. However, the potential for increased recovery room monitoring or treatment of emergence reactions with ketamine-midazolam must be considered in the overall cost-benefit analysis. In the present study, the comparable recovery times and low incidence of emergence reactions suggest that the ketamine-midazolam combination is a cost-effective alternative to propofol for induction in cardiac patients.

The generalizability of these findings to other patient populations and clinical settings deserves consideration. The study population consisted of cardiac patients (ASA class II-III) undergoing elective non-cardiac surgery at a single tertiary care hospital in Lahore, Pakistan. The results may not be directly applicable to patients with more severe cardiac disease (ASA class IV), those undergoing emergency surgery, or those with specific cardiac pathologies such as severe valvular stenosis or obstructive cardiomyopathy. However, the physiological principles underlying the observed hemodynamic differences are likely to apply broadly, and the findings provide valuable guidance for the anesthetic management of cardiac patients in similar clinical settings.

Several limitations of this study should be acknowledged. First, the study was quasi-experimental rather than randomized, which

introduces the potential for selection bias despite the use of a computer-generated allocation sequence. However, the comparability of baseline characteristics between groups suggests that the allocation was effective in balancing potential confounders. Second, the study was conducted at a single center, which may limit the generalizability of the findings. Multicenter studies would be needed to confirm these results in different patient populations and clinical settings. Third, the study did not include blinding of the anesthesiologists to the group allocation, which could introduce performance bias. However, the use of objective outcome measures such as blood pressure, heart rate, and perfusion index minimizes the risk of measurement bias. Fourth, the study did not assess long-term outcomes such as myocardial infarction, stroke, or mortality, which would be important to determine whether the observed hemodynamic differences translate into improved clinical outcomes. Larger studies with longer follow-up would be needed to address these important questions. Fifth, the sample size of 120 patients, while adequate to detect differences in hemodynamic parameters, may not have been sufficient to detect differences in less common adverse events or to perform subgroup analyses. Finally, the study did not include a group receiving ketamine without midazolam, which would have helped to isolate the specific contribution of midazolam to the hemodynamic and safety profile. Despite these limitations, this study provides important evidence that the combination of ketamine and midazolam offers superior hemodynamic stability compared to propofol for induction of anesthesia in cardiac patients undergoing non-cardiac surgery. The findings are consistent with the known pharmacological properties of these agents and with previous studies comparing propofol and ketamine-based regimens. The study adds to the growing body of literature supporting the use of ketamine-based induction in high-risk cardiac patients.

The clinical implications of these findings are significant. The induction of anesthesia is a critical period during which hemodynamic instability can precipitate serious cardiovascular complications, including myocardial ischemia, arrhythmias, and cardiac arrest. In cardiac patients, who have limited cardiovascular reserve and are already at increased risk of perioperative complications, maintaining hemodynamic stability during induction is paramount. The results of this study suggest that the ketamine-midazolam combination is a safe and effective alternative to propofol for induction in these patients, offering better blood pressure maintenance, improved peripheral perfusion, and a lower incidence of hypotension. The comparable recovery profile and acceptable safety profile further support the use of this combination in clinical practice.

Future research should focus on several important areas. Larger, multicenter randomized controlled trials are needed to confirm these findings and to assess long-term outcomes. Studies comparing

different doses of ketamine and midazolam would help to identify the optimal dose combination that maximizes hemodynamic stability while minimizing side effects. The role of perfusion index as a guide to intraoperative hemodynamic management deserves further investigation, particularly in cardiac patients where maintaining adequate perfusion is critical. Finally, cost-effectiveness analyses would be valuable to guide resource allocation in healthcare settings with limited budgets.

CONCLUSION

This comparative study demonstrates that induction of anesthesia with the combination of ketamine (1 mg/kg) and midazolam (0.05 mg/kg) provides superior hemodynamic stability compared to propofol (2 mg/kg) in cardiac patients undergoing non-cardiac surgery. The ketamine-midazolam group maintained significantly higher systolic blood pressure, diastolic blood pressure, mean arterial pressure, and perfusion index throughout the post-induction period, with a significantly lower incidence of hypotension and reduced requirement for vasopressor support. Recovery time and length of hospital stay were comparable between groups, and the incidence of adverse events was acceptable in both groups.

The findings suggest that the ketamine-midazolam combination is a safe, effective, and cost-effective alternative to propofol for induction of anesthesia in cardiac patients. The hemodynamic benefits of this regimen, particularly the preservation of blood pressure and peripheral perfusion, are likely to reduce the risk of perioperative cardiovascular complications in this high-risk patient population. The use of midazolam effectively attenuates the psychotomimetic side effects of ketamine without compromising its hemodynamic advantages, making this combination a practical and attractive option for clinical practice.

Based on these findings, we recommend that the combination of ketamine and midazolam be considered as a first-line induction agent in cardiac patients undergoing non-cardiac surgery, particularly in resource-limited settings where propofol may be less accessible or more costly. Further research with larger sample sizes and longer follow-up is warranted to confirm these findings and to assess the impact on long-term clinical outcomes.

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