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Assessment of Cardiac Biomarkers Following Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis

By

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Abstract

Transcatheter aortic valve implantation (TAVI) has emerged as a transformative intervention for patients with severe aortic stenosis (AS), particularly those deemed high-risk for open surgery. The hemodynamic and biochemical responses following TAVI remain a critical area of investigation, especially in the context of perioperative management strategies that may modulate myocardial stress and injury. This experimental study aimed to evaluate the influence of sub-anesthetic dosing of ketamine on post-procedural cardiac biomarker profiles, including high-sensitivity troponin T (hs-TnT), creatine kinase-MB (CK-MB), and N-terminal pro B-type natriuretic peptide (NT-proBNP), in patients undergoing TAVI.

A total of 84 patients were randomly divided into two groups: a sub-anesthetic ketamine group (0.3 mg/kg bolus followed by 0.1 mg/kg/h infusion) and a standard sedation group without ketamine. Biomarker levels were measured preoperatively, and at 6 and 24 hours post-procedure. Results revealed statistically significant reductions in hs-TnT and NT-proBNP levels in the ketamine group at both time points ($p<0.001$), suggesting reduced myocardial injury and stress. No significant difference in CK-MB was observed between the groups.

These findings underscore the cardioprotective potential of sub-anesthetic ketamine in mitigating biochemical injury following TAVI. This study introduces a novel adjunctive strategy to optimize TAVI outcomes by leveraging sub-anesthetic modulation of perioperative myocardial stress.

Keywords: *Transcatheter Aortic Valve Implantation, Cardiac Biomarkers, Sub-Anesthetic Ketamine*

Introduction

Transcatheter aortic valve implantation (TAVI) has rapidly established itself as a less invasive yet durable therapeutic option for severe aortic stenosis (AS), particularly in older or high-risk surgical candidates. While hemodynamic improvement post-TAVI is well established, the underlying biochemical responses—especially perioperative myocardial injury marked by rises in high-sensitivity troponin (hs-Tn) and natriuretic peptides—remain incompletely characterized, limiting both prognostic insight and perioperative optimization strategies.1-4

Myocardial injury following non-cardiac interventions is increasingly recognized as a critical determinant of postoperative outcomes. Contemporary guidelines underscore

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that even modest perioperative elevations in cardiac biomarkers, particularly hs-Tn and NT-proBNP, are associated with substantial short- and long-term mortality, irrespective of overt clinical ischemia. Specifically, perioperative hs-Tn elevations may reflect multifactorial myocardial stress—including hemodynamic fluctuations, sympathetic overactivity, and systemic inflammation—rather than classic focal ischemia . In the setting of TAVI, these pathophysiologic mechanisms are particularly relevant; rapid valve deployment may precipitate transient myocardial strain and endothelial activation, frequently reflected by biomarker kinetics, even in the absence of epicardial coronary compromise.5-7

Anesthetic adjuncts have emerged as promising modulators of this peri-TAVI myocardial insult. Ketamine, administered at sub-anesthetic doses, exhibits a unique sympathomimetic profile that supports hemodynamic stability during periods of stress. Low-dose ketamine not only preserves arterial pressure and cardiac output but also attenuates inflammatory cascades, as evidenced by reduced cytokine release in thoracic and non-cardiac surgical models . In recent pulmonary lobectomy trials, low-dose S-ketamine significantly lowered circulating levels of hs-cTnT, BNP, and inflammatory mediators (IL-6, IL-8, TNF-α), suggesting a direct cardioprotective effect beyond simple analgesia. Importantly, the study showed statistically significant reductions in all measured biomarkers at both 24 and 48 h postoperatively ($p < 0.05$), while maintaining stable mean arterial pressure and opioid consumption —an optimal balance of efficacy and safety.8-10

Despite these encouraging findings, similar investigations within TAVI cohorts are lacking. Given that TAVI patients are characteristically older, frailer, and at high risk of perioperative myocardial injury, there is a critical unmet need for interventional strategies that mitigate biomarker surges. Ketamine's hemodynamic and anti-inflammatory actions make it a compelling candidate to fill this gap. Illustratively, recent perioperative cardioprotection studies—such as those using dexmedetomidine—demonstrate reduced hs-TnI and attenuated inflammatory profiles, with improved clinical recovery , suggesting that anesthetic modulation can effectively reduce surgical myocardial injury.

Furthermore, expert guidelines now recommend routine perioperative hs-Tn and NT-proBNP monitoring in patients undergoing high-risk procedures (portailvasculaire.fr). This shift toward biomarker-driven surveillance enhances the potential to detect and ameliorate subclinical myocardial damage. However, no protocolized pharmacologic approach exists to actively reduce biomarker elevation in the TAVI setting.

Consequently, this study was conceived as the first randomized, experimental investigation evaluating low-dose ketamine's impact on cardiac biomarker trajectories post-TAVI. By measuring hs-TnT, CK-MB, and NT-proBNP at defined perioperative time points (pre-procedure, 6 h, and 24 h), the trial aimed to determine whether sub-anesthetic ketamine reduces biochemical evidence of myocardial stress compared with standard sedation protocols.

From a mechanistic standpoint, ketamine may confer myocardial benefit by maintaining systemic vascular resistance, supporting coronary perfusion pressure during rapid pacing and valve deployment, and attenuating inflammatory cytokine release—potentially disrupting the "two-hit" pathway of cardiomyocyte injury during procedural stress . Moreover, its established safety at low doses, including minimal respiratory depression and hemodynamic tolerability, makes it well-suited for elderly, comorbid patients.

In summary, this introduction establishes the clinical significance of peri-TAVI myocardial injury, identifies sub-anesthetic ketamine as a plausible intervention based on recent biomarker modulation studies, and positions this experiment at the forefront of perioperative cardiovascular research. References have been limited to studies from 2022–2024 to ensure incorporation of the most current evidence. The ensuing sections will delineate the methodology, present the statistically significant biomarker outcomes, and discuss the implications and future directions of these findings.

Methodology

This experimental, randomized, controlled study was conducted between January 2023 and February 2024 at a tertiary cardiovascular center FMH Lahore. A total of 84 patients diagnosed with severe symptomatic aortic stenosis and scheduled for elective transfemoral transcatheter aortic valve implantation (TAVI) were enrolled. The sample size was calculated using Epi Info (version 7.2.5) based on preliminary data from pilot observations, assuming an anticipated effect size of 0.8 in hs-TnT reduction with a power of 80% and α error of 0.05. A minimum of 40 participants per group was required to detect statistically significant differences in post-procedure biomarker levels. Participants were randomly assigned, using computer-generated blocks, to one of two groups: the control group receiving standard sedation with midazolam and fentanyl alone, and the intervention group receiving a low-dose ketamine regimen (initial bolus of 0.3 mg/kg followed by continuous infusion at 0.1 mg/kg/h until valve deployment), in addition to standard sedatives.

Eligibility criteria included patients aged between 65 and 90 years, with echocardiographically confirmed severe aortic stenosis (aortic valve area <1.0 cm^2 and/or mean gradient >40 mmHg), preserved or mildly reduced left ventricular ejection fraction (≥40%), and preoperative clearance for conscious sedation. Patients were excluded if they had prior myocardial infarction within 30 days, uncontrolled arrhythmia, end-stage renal disease (eGFR <30 ml/min/1.73 m^2), known allergy to ketamine, psychiatric comorbidity, or inability to provide informed verbal consent. Institutional Review Board approval was obtained before recruitment, and all participants gave documented verbal consent in accordance with ethical guidelines for minimal-risk pharmacologic studies.

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Baseline demographics, echocardiographic parameters, and comorbidities were recorded. Biomarkers including high-sensitivity troponin T (hs-TnT), creatine kinase-MB (CK-MB), and NT-proBNP were measured preoperatively (within 4 hours prior to TAVI), and subsequently at 6 and 24 hours post-procedure. Venous samples were analyzed in a centralized lab using standardized electrochemiluminescence immunoassays (ECLIA). The laboratory staff was blinded to group allocation.

Procedural sedation and monitoring were standardized across all patients. Valve deployment was performed via transfemoral access using balloon-expandable or self-expanding prostheses under conscious sedation. Hemodynamic parameters, including mean arterial pressure, heart rate, and oxygen saturation, were continuously monitored. No significant hemodynamic complications requiring conversion to general anesthesia occurred in either group.

Statistical analysis was performed using SPSS version 26.0. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD), and between-group comparisons were made using independent-samples t-tests. Categorical variables were compared using chi-square tests. Repeated-measures ANOVA was used to evaluate temporal changes in biomarker levels within and between groups. A two-tailed p-value <0.05 was considered statistically significant. All analyses were conducted on an intention-to-treat basis.

Results

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n=84)

Variable	Control Group (n=42)	Ketamine Group (n=42)	p-value
Age (years)	77.6 ± 6.1	78.2 ± 5.8	0.62
Male (%)	52.4	54.8	0.83
BMI (kg/m²)	26.4 ± 3.2	25.9 ± 3.5	0.49
Hypertension (%)	85.7	83.3	0.75
Diabetes Mellitus (%)	33.3	35.7	0.82
LVEF (%)	55.2 ± 6.9	54.7 ± 7.1	0.71
Baseline hs-TnT (ng/L)	16.8 ± 5.4	17.2 ± 5.6	0.74
Baseline NT-proBNP (pg/mL)	974 ± 238	998 ± 221	0.66
CK-MB (U/L)	22.4 ± 5.3	23.1 ± 5.7	0.57

Demographic and baseline biomarker characteristics were statistically comparable between groups, confirming homogeneity prior to intervention (p > 0.05).

Table 2: Post-Procedure Biomarker Levels at 6 and 24 Hours

Biomarker	Timepoint	Control Group	Ketamine Group	p-value
hs-TnT (ng/L)	6 h	84.2 ± 15.6	63.9 ± 14.8	<0.001
	24 h	76.3 ± 14.2	56.7 ± 12.6	<0.001
NT-proBNP (pg/mL)	6 h	1604 ± 332	1226 ± 285	<0.001
	24 h	1489 ± 308	1171 ± 264	<0.001
CK-MB (U/L)	6 h	38.7 ± 7.4	37.2 ± 7.1	0.29
	24 h	35.1 ± 6.8	34.2 ± 6.6	0.41

Significant reductions in hs-TnT and NT-proBNP were observed in the ketamine group at both 6 and 24 hours post-TAVI (p < 0.001). No statistically significant difference was found for CK-MB at either time point (p > 0.05).

Table 3: Temporal Change in Biomarker Levels Within Groups

Biomarker	Group	Pre-op	6 h Post-op	24 h Post-op	p (ANOVA)
hs-TnT (ng/L)	Control	16.8 ± 5.4	84.2 ± 15.6	76.3 ± 14.2	<0.001
	Ketamine	17.2 ± 5.6	63.9 ± 14.8	56.7 ± 12.6	<0.001
NT-proBNP (pg/mL)	Control	974 ± 238	1604 ± 332	1489 ± 308	<0.001
	Ketamine	998 ± 221	1226 ± 285	1171 ± 264	<0.001
CK-MB (U/L)	Control	22.4 ± 5.3	38.7 ± 7.4	35.1 ± 6.8	<0.001
	Ketamine	23.1 ± 5.7	37.2 ± 7.1	34.2 ± 6.6	<0.001

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Within-group analysis showed significant rises in all biomarkers post-procedure ($p < 0.001$), but the magnitude of change was significantly lower in the ketamine group for hs-TnT and NT-proBNP.

Discussion

The findings of this study demonstrate that administration of sub-anesthetic doses of ketamine during TAVI significantly reduces myocardial stress as reflected by lower post-procedure hs-TnT and NT-proBNP levels. These results align with recent literature identifying myocardial biomarker elevation as a strong predictor of 30-day and 1-year mortality post-TAVI, independent of overt myocardial infarction or ECG changes[16]. The attenuation of this elevation suggests a direct perioperative myocardial protective effect of ketamine that has not been explored in TAVI-specific populations until now.11-13

The reduced troponin levels observed in the ketamine group likely reflect mitigation of myocardial strain and microinjury during valve deployment and rapid ventricular pacing. Several mechanistic studies have documented the vasopressor-sparing and sympathomimetic properties of ketamine, which may prevent transient hypoperfusion of coronary beds during procedural hypotension.14-17 Moreover, ketamine's inhibition of N-methyl-D-aspartate (NMDA) receptors modulates the excitotoxic cascade and suppresses systemic catecholamine surges, thereby reducing myocardial oxygen demand.18-20 These pathophysiologic effects are particularly relevant in elderly TAVI cohorts with limited coronary reserve and vulnerable myocardium.

Additionally, the reduction in NT-proBNP, a marker of myocardial wall stress and subclinical heart failure, supports the notion that ketamine may attenuate myocardial loading conditions perioperatively. Previous work has shown that elevated NT-proBNP post-TAVI predicts prolonged hospitalization, increased readmissions, and impaired reverse remodeling. Therefore, the significantly lower NT-proBNP levels in the ketamine group may imply not only myocardial protection but also improved early recovery trajectories, though longer-term data are required to confirm this hypothesis.

The lack of significant difference in CK-MB levels may be explained by the lower sensitivity and tissue specificity of this marker compared to hs-TnT. CK-MB primarily reflects gross necrosis, which is less common in contemporary TAVI settings, especially with conscious sedation and hemodynamic optimization. Thus, the absence of CK-MB difference reinforces that ketamine's benefit lies in limiting myocardial strain rather than preventing infarction per se. It further supports the use of high-sensitivity troponins as more reliable markers of subtle myocardial injury in modern interventional cardiology protocols.

These results are also consistent with emerging data from non-cardiac surgical models. For example, a recent randomized trial in patients undergoing thoracic surgery demonstrated that low-dose ketamine significantly reduced postoperative hs-TnT, IL-6, and TNF-α levels[22]. Likewise, in patients undergoing major abdominal surgery, ketamine infusion was associated with improved perioperative hemodynamic stability and reduced markers of systemic inflammation. While these studies were conducted in non-cardiac settings, they collectively underscore ketamine's systemic anti-inflammatory and cardioprotective profile.

Importantly, ketamine administration was not associated with adverse hemodynamic events or need for general anesthesia conversion in this study, reaffirming its safety in elderly, high-risk populations. Given that conscious sedation is now the default strategy for transfemoral TAVI due to its association with reduced morbidity and faster recovery, adjunctive agents that preserve hemodynamic stability and minimize myocardial stress are increasingly sought. This study provides early evidence that low-dose ketamine may fill this pharmacologic gap, with the added benefit of preserving sedation depth and analgesia.

This research addresses a critical knowledge gap in TAVI anesthesia by being the first to quantify the cardioprotective effects of ketamine using objective biochemical endpoints. Prior investigations into anesthetic strategies during TAVI have focused primarily on procedural outcomes, with little emphasis on biomarker-driven subclinical myocardial injury. Future studies should explore dose-response relationships, investigate long-term prognostic implications of biomarker suppression, and consider combining ketamine with other modulators such as dexmedetomidine or lidocaine. Such multidrug protocols may offer synergistic protection, particularly in frail cohorts with elevated preoperative risk**.**

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