



Ketamine as a Neuroprotective Intervention to Prevent Early Post-CABG Delirium: A Triple-Blind Randomized Clinical Trial

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Abstract

Background: Postoperative delirium frequently occurs after coronary artery bypass graft (CABG) surgery, negatively impacting patient recovery and outcomes. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist with analgesic and anti-inflammatory effects, is considered a potential strategy for delirium prevention.

Objectives: This study examines the efficacy of intravenous ketamine administered during anesthesia induction in reducing postoperative delirium among CABG patients.

Methods: A triple-blind, randomized, placebo-controlled clinical trial was performed on 92 patients scheduled for elective CABG surgery. Participants were randomly allocated to receive either ketamine (0.5 mg/kg, n = 46) or an equivalent placebo dose at anesthesia induction (n = 46). Delirium was assessed at 24 and 48 hours postoperatively using the Intensive Care Delirium Screening Checklist (ICDSC), covering the peak period of delirium incidence after CABG. Due to clinical workflow and resource constraints, long-term follow-up beyond 48 hours was not conducted. Statistical analyses included chi-square tests and *t*-tests, conducted using SPSS version 19, with a two-sided significance level of 0.05.

Results: Baseline demographic and surgical characteristics were similar between groups. Delirium incidence at 24 hours was significantly lower in the ketamine group (2.2%) compared to the control group (17.4%) (*P* = 0.045). At 48 hours, the rates were 4.4% in the ketamine group versus 26.1% in controls (*P* = 0.038). These preliminary findings suggest a possible association between ketamine and reduced early delirium, though small event numbers and short follow-up limit definitive conclusions.

Conclusions: Ketamine was associated with a lower incidence of early postoperative delirium; however, the small number of delirium events limits the strength of this conclusion. Larger trials with extended follow-up and comprehensive safety monitoring are essential before clinical implementation.

Keywords: Delirium, Coronary Artery Bypass, Ketamine, Postoperative Delirium

1. Background

With the global rise in life expectancy and the increasing prevalence of chronic diseases, the incidence of coronary artery disease has surged, necessitating more frequent reliance on surgical interventions such as coronary artery bypass graft (CABG). According to the

World Health Organization, in Iran, more than 70 percent of deaths are due to chronic diseases, and of this amount, 42 percent are related to cardiovascular issues (1, 2). While CABG is a well-established treatment for severe angina, it carries a significant risk of postoperative delirium, which can complicate patient management and extend hospitalization (3). Compared

to non-cardiac surgeries, it seems there are more specific factors in cardiac surgeries that may affect the incidence of postoperative delirium (4). The incidence of delirium in patients undergoing CABG surgery ranges between 8 to 54 percent (5). Delirium causes an increase in postoperative morbidity and mortality and extends long-term care needs (6).

Ketamine, a widely recognized N-methyl-D-aspartate (NMDA) receptor antagonist that primarily influences glutamate signaling, may contribute to a reduction in postoperative delirium by modulating inflammatory pathways and mitigating excitotoxicity. These properties suggest its potential as a beneficial adjunct in the perioperative management of patients undergoing CABG (7). However, the current body of research on ketamine's role in preventing postoperative delirium in cardiac surgery remains limited and methodologically diverse, making it difficult to draw definitive conclusions about its efficacy and optimal dosing. Additionally, inconsistencies in the results of previous studies highlight the necessity for well-designed randomized controlled trials to clarify ketamine's potential benefits in this context.

2. Objectives

This study aims to assess the effectiveness of intravenous ketamine administration during anesthesia induction in reducing postoperative delirium in CABG patients.

3. Methods

We conducted this randomized controlled trial following the CONSORT guidelines (2010) (Figure 1). This study was approved by our institutional ethics committee (IR.IUMS.REC.1402.833) and registered in clinical trials (IRCT20231021059795N1). The study population included patients referred to the Research and Treatment Center of Hazrat Rasool Akram (PBUH) at Iran University of Medical Sciences for CABG surgery between March 2024 and January 2025, who met the study eligibility criteria. Prior to enrollment, informed consent was obtained from all participants.

3.1. Sample Size

The sample size was estimated based on preliminary data from a pilot study, in which postoperative delirium occurred in 35% of patients in the placebo group and 0% in the ketamine group (8). To detect a similar difference with 80% power and a two-sided significance level of 0.05, a two-sample z-test for independent proportions was performed using G*Power 3.1 software. This

calculation indicated that 42 patients per group would be required. Considering a potential 10% attrition rate, the final sample size was increased to 50 patients per group, resulting in a total of 100 participants.

Although the original pilot study used 90% power (8), we chose 80% in the current study to balance feasibility with statistical rigor in our clinical setting. Although the initial sample size calculation indicated 100 participants, due to 5 patients declining participation and 3 additional patients excluded after randomization, a total of 92 patients (46 per group) were included in the final analysis (Figure 1).

3.2. Eligibility Criteria for Participants

Eligible participants were adults aged 40 to 80 years, classified as American Society of Anesthesiologists (ASA) physical status II or III, scheduled to undergo isolated CABG surgery. To ensure clinical homogeneity and minimize confounding related to surgical complexity, only patients undergoing procedures with an expected duration of 3 - 4 hours were considered; operative times exceeding 6 hours were prespecified as an exclusion criterion (9, 10). Additionally, all included patients were required to receive comparable numbers of grafts and be managed by standardized perioperative care teams.

Patients were excluded if they had a history of postoperative delirium, preexisting psychiatric disorders, or current use of antipsychotic medications. Other exclusion criteria included self-reported or documented delirium within seven days following any prior surgery, chronic alcohol consumption, cerebrovascular disease, or a Body Mass Index (BMI) greater than 38 kg/m². Patients scheduled for concurrent valve surgery were also excluded to maintain procedural uniformity.

3.3. Randomization

Regarding the sampling method, participants were selected through convenience sampling and randomized into two groups using block randomization with block sizes of four (e.g., AABB, ABAB, BBAA, etc.), generated via Microsoft Excel. The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes and managed by an independent epidemiologist to ensure allocation concealment.

3.4. Blinding

To ensure blinding, the assistant researcher responsible for data collection and the statistician analyzing the data were unaware of the group

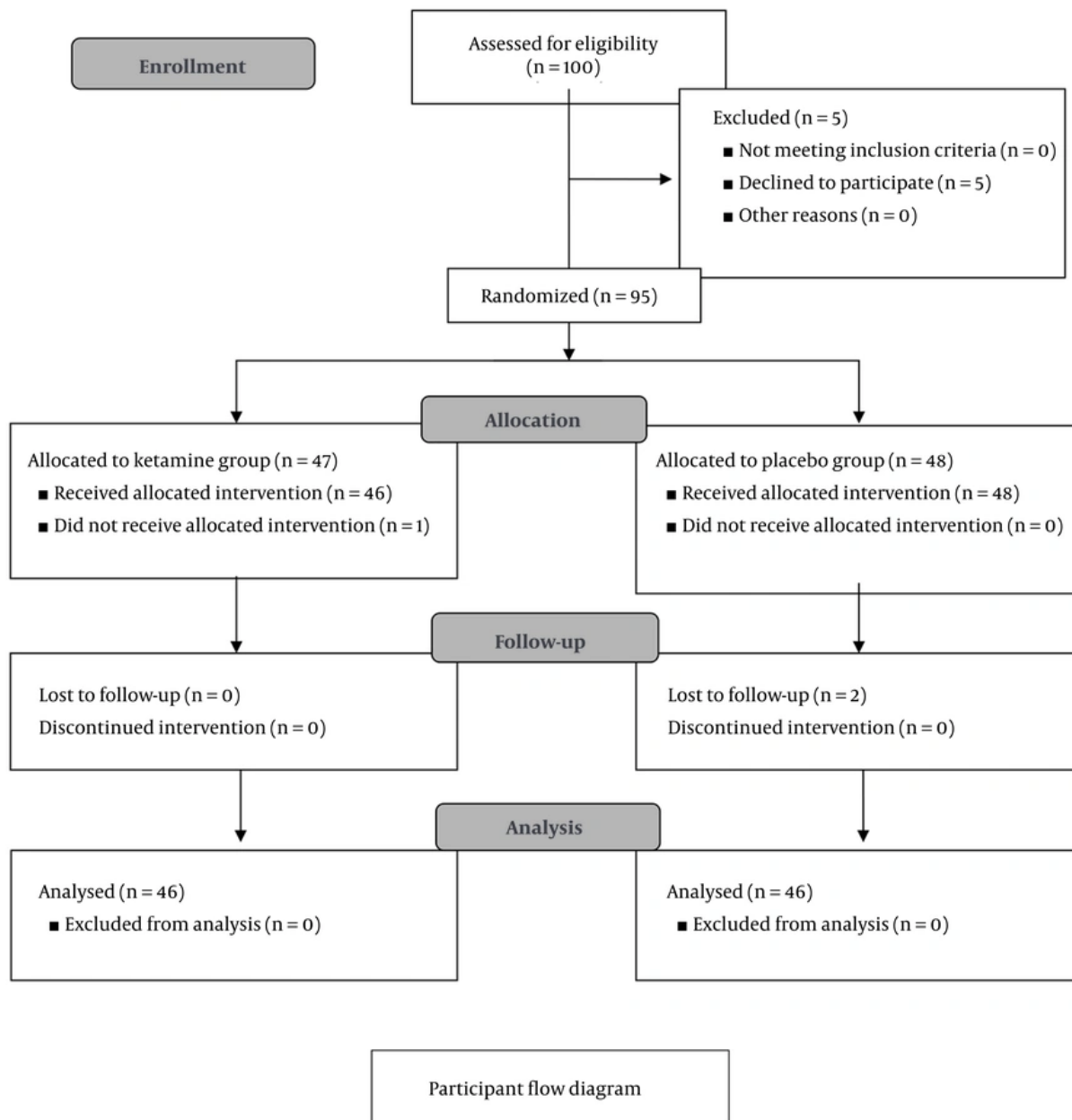


Figure 1. CONSORT 2010 flow diagram

assignments. Additionally, the clinicians and nurses working in the recovery and operating rooms were also blinded to the group allocations. The study implemented a triple-blind approach, in which neither the patients, sample collector, nor statistical analyst were aware of the medication prescribed.

3.5. Interventions

The study drugs were placed in sealed and coded envelopes and then provided to anesthesiologists who were not part of the research team. Following the induction of anesthesia with a loading dose of

midazolam (0.05 - 0.5 mg/kg), fentanyl (2 - 10 mcg/kg), and atracurium (0.5 mg/kg), the intervention drug was administered. Patients in the intervention group received ketamine at a dose of 0.5 mg/kg, up to a maximum of 50 mg, infused in 100 cc saline over a maximum of 5 minutes. The control group was administered an equal volume of normal saline through infusion over the same duration. To reduce potential bias, the questionnaires were coded in a manner that kept both participants and researchers involved in data collection and analysis unaware of the group allocations.

3.6. Monitoring

After anesthesia, maintenance was achieved through continuous infusion of fentanyl, atracurium, and midazolam at a rate of 10 - 15 cc/min for all patients. Monitoring and cerebral oximetry continued during anesthesia. Activated clotting time above 480 seconds was maintained with heparin at a dose of 300 - 400 IU/kg, and its effect was reversed at the end of surgery with 1 mg of protamine sulfate per 100 units of heparin. Hypothermia was maintained with a core temperature of 30 - 34°C (8). Mean arterial pressure was kept between 55 to 70 mmHg, PaO₂ at 150 - 250 mmHg, and PaCO₂ at 35 - 45 mmHg during cardiopulmonary bypass (CPB). Blood transfusions were performed as needed, with the number and type of units recorded. Separation from CPB was assisted with epinephrine, dobutamine, or norepinephrine as required. Upon completion of the surgery, the patient was moved to the intensive care unit (ICU), where sedation was maintained using a propofol infusion at a dose of 50 - 100 mcg/kg/min. Monitoring and mechanical ventilation were continued, and environmental factors such as light, temperature, and noise in the cardiac ICU were standardized to ensure consistency for all patients.

3.7. Measurement Tools

Delirium was assessed at 24 and 48 hours postoperatively, as the peak incidence of postoperative delirium after CABG surgery typically occurs within this window. This study used an instrument with 8 sections to collect demographic information, surgery duration, and CPB time. Delirium was evaluated using the intensive care delirium screening checklist (ICDSC), originally introduced in 2001 and later validated and standardized by Torshizi *et al.* in 2016. The tool demonstrated a Cronbach's alpha reliability coefficient of 0.83 and a split-half reliability coefficient of 0.72 (11). In our study, the checklist was revalidated by two independent evaluators on a separate cohort of 30

patients who were not part of the main study sample. This validation phase was conducted prior to data collection to assess inter-observer reliability, yielding an intraclass correlation coefficient of 0.85. These 30 patients were excluded from the final analysis after the validation process was completed.

Follow-up was limited to 48 hours due to the transition of patients from the cardiac ICU to general wards, where standardized delirium screening using the ICDSC is not routinely feasible. Additionally, resource limitations, including availability of trained nursing staff for consistent assessment, precluded extended monitoring.

3.8. Statistical Analysis

Categorical variables were summarized as frequencies and percentages to describe the demographic and clinical characteristics of the participants. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. Independent-samples *t*-tests were used to compare continuous variables between groups. Welch's correction was applied when Levene's test indicated unequal variances or when the group sizes were substantially different, such as in comparisons between delirious (*n*=10) and non-delirious (*n*=82) patients. The Mann-Whitney U test was used as a sensitivity analysis. Results are reported as mean ± SD for each group, along with mean differences and 95% confidence intervals. For categorical variables, the chi-square test was employed, and Fisher's exact test was applied when expected cell frequencies were below 5. Effect sizes were reported with 95% confidence intervals. Univariate and multivariate logistic regression analyses were performed to examine the association of intraoperative factors with delirium, adjusting for age, sex, hypertension, and diabetes. Statistical analyses were conducted using SPSS software version 19, with a significance threshold set at *P* < 0.05.

4. Results

A total of 92 patients were included in the final per-protocol analysis, with 46 participants in each group (ketamine and control). Of the 100 patients initially screened for eligibility, 5 declined to participate and were excluded prior to randomization. Following randomization (*n* = 95), 3 additional patients were excluded from the final analysis: One patient in the ketamine group did not receive the allocated intervention, and 2 patients in the placebo group were lost to follow-up. Per-protocol analysis was conducted; intention-to-treat (ITT) analysis was not performed due

to post-randomization exclusions and missing outcome data.

The baseline demographic and clinical characteristics, including age, sex, history of ICU admission, hypertension (HTN), diabetes, and ASA class, were compared between the two groups. No statistically significant differences were observed for these variables ($P > 0.05$ for all comparisons), indicating insufficient evidence to reject the null hypothesis of no difference between groups. However, this does not confirm complete equivalence or homogeneity, as undetected differences may exist due to factors such as limited statistical power.

In terms of gender distribution, the majority of participants were male in both the control group (63.3%, $n = 29$) and the ketamine group (71.7%, $n = 33$), with males comprising 67.4% ($n = 62$) of the total sample. Regarding age distribution, the majority of participants were aged 40 - 60 years (44.6%, $n = 41$), followed by 60 - 70 years (35.9%, $n = 33$), and 70 - 80 years (22.8%, $n = 21$). The distributions of age, gender, ICU admission history, and comorbidities such as HTN and diabetes were similar across both groups (Table 1).

4.1. Incidence of Postoperative Delirium

At 24 hours post-surgery, delirium occurred in 8 patients (17.39%) in the control group and 1 patient (2.17%) in the ketamine group, corresponding to a relative risk (RR) of 0.13 (95% CI, 0.02 - 0.99) and an absolute risk reduction (ARR) of 15.22% [number needed to treat (NNT)=7]. After Bonferroni correction for two primary time-point comparisons, the difference remained significant ($P=0.022$). By 48 hours, delirium was present in 12 patients (26.09%) and 2 patients (4.35%) in the control and ketamine groups, respectively [RR=0.17 (95% CI, 0.04 - 0.73); ARR=21.7%; NNT=5 (95% CI, 3 - 12)], with the adjusted P -value=0.019 (Figure 2). These findings indicate a consistent and clinically meaningful decrease in early postoperative delirium with ketamine administration. Only one patient in the ketamine group developed delirium within 24 hours, supporting a potential protective effect, though subgroup analyses were not performed due to limited power.

Regarding other parameters presented in Table 2, no statistically significant differences were observed between groups for mean arterial pressure (97.99 ± 8.45 mmHg vs. 98.91 ± 9.13 mmHg; $P = 0.635$), duration of surgery (340.68 ± 29.24 min vs. 344.18 ± 31.56 min; $P = 0.513$), CPB time (91.21 ± 15.67 min vs. 89.11 ± 14.45 min; $P = 0.578$), or cross-clamp time (54.12 ± 12.43 min vs. 57.32 ± 13.26 min; $P = 0.412$). These results suggest a potential

association between ketamine administration at the induction of anesthesia and reduced postoperative delirium incidence.

4.2. Surgical Duration and Intraoperative Variables

Intraoperative variables were compared between delirious and non-delirious patients across the entire sample (Table 3). Delirious patients tended to have longer surgical durations and lower ejection fractions. However, these differences should be interpreted with caution, as confidence intervals were wide and the small number of delirious cases ($n = 10$) substantially limits the statistical power of these comparisons. Although point estimates suggest potential clinical relevance in the context of CABG surgery, definitive conclusions cannot be drawn.

It should be noted that only one patient in the ketamine group developed delirium. Therefore, subgroup analyses for this single patient are not statistically meaningful, and the results should be interpreted with caution. The reported P -values in Table 3 correspond to overall comparisons between delirious and non-delirious patients, regardless of treatment allocation, and not within each treatment group.

Cardiopulmonary bypass and aortic cross-clamp times followed a similar pattern, with delirious patients showing slightly shorter averages compared with non-delirious patients; however, none of these differences were statistically significant (all $P > 0.05$).

5. Discussion

Coronary artery bypass graft surgery is a widely recognized procedure for improving cardiac function and enhancing patients' quality of life (12). However, it is also associated with a considerable risk of postoperative delirium, which remains a significant clinical concern (13). Ketamine, an N-methyl-D-aspartic acid antagonist that modulates noradrenergic and serotonergic neurons in the locus coeruleus, is an anesthetic with analgesic and anti-inflammatory properties. It aids postoperative recovery and satisfaction in cardiac surgery patients by reducing C-reactive protein and interleukin-6 levels. Recent studies have indicated that the impact of ketamine administration on the incidence of delirium following CABG surgery is still not well-defined (14, 15).

Hence, additional studies are required in this field to enhance postoperative recovery and mitigate the potential risks associated with ketamine administration. In this study, we opted to administer ketamine via infusion at a dose of 0.5 mg/kg, not

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants ^{a, b}

Variables and Category	Total (n = 92)	Control (n = 46)	Ketamine (n = 46)	P-Value (χ^2)
Age (y)				0.493 ($\chi^2 = 1.415$)
40 - 60	41 (44.6)	18 (39.1)	23 (50.0)	
60 - 70	33 (35.9)	20 (43.4)	13 (28.3)	
70 - 80	18 (19.6)	8 (17.3)	10 (21.7)	
Gender				0.584 ($\chi^2 = 0.30$)
Male	62 (67.4)	29 (63.3)	33 (71.7)	
Female	30 (32.6)	17 (36.7)	13 (28.3)	
ICU admission history				1.00 ^{c, d}
No	91 (98.9)	46 (100)	45 (97.8)	
Yes	1 (1.1)	0 (0)	1 (2.2)	
Hypertension				0.706 ^c
No	12 (13.0)	8 (17.3)	4 (8.6)	
Yes	80 (87.0)	38 (82.6)	42 (91.3)	
Diabetes mellitus				1.000 ($\chi^2 = 0.00$)
No	56 (60.9)	28 (60.9)	28 (60.9)	
Yes	36 (39.1)	18 (39.1)	18 (39.1)	
ASA physical status				1.000
II	10 (10.9)	6 (13.0)	4 (8.7)	
III	82 (89.1)	40 (87.0)	42 (91.3)	

Abbreviations: χ^2 , chi-square; ASA, American Society of Anesthesiologists; ICU, intensive care unit.

^a Values are expressed as No (%).

^b χ^2 values are Pearson chi-square statistics unless otherwise specified. When expected cell counts were < 5, Fisher's exact test P-values were reported

^c Fisher's exact

^d Due to the very low occurrence of ICU admission (only one event in total), Fisher's exact test reports P=1.00, reflecting the equal probability of this event across groups.

exceeding 50 mg, over a maximum duration of 5 minutes during anesthesia induction. This approach was designed to leverage its anti-inflammatory and neuroprotective properties while minimizing the risk of adverse effects typically associated with higher dosages (16-18).

The findings of this study suggest that intravenous ketamine administration during anesthesia induction significantly lowered the incidence of postoperative delirium in patients undergoing CABG surgery. Specifically, ketamine showed a protective effect against delirium at both 24 and 48 hours after surgery, highlighting its potential as an effective intervention in this high-risk group. This result is particularly important considering the considerable negative impact of delirium on patient outcomes, including extended ICU stays, elevated healthcare costs, and long-term cognitive deterioration. Although ketamine was associated with a lower delirium incidence, event counts were small and the study remained moderately powered. Effect size estimates (RR=0.17, NNT=5) suggest potential clinical benefit, but confirmatory multicenter trials are required. The exploratory nature and limited

statistical power of subgroup analyses also warrant cautious interpretation.

The reduction in delirium incidence with ketamine use aligns with its pharmacological properties, including its NMDA receptor antagonism and anti-inflammatory effects (8, 15).

Our study aligns with the findings of Hudetz et al. and Siripoonyothai and Sindhvananda (8, 13) Hudetz et al. demonstrated that administering ketamine at a dose of 0.5 mg/kg during anesthesia induction for cardiac surgery with CPB effectively reduced the incidence of postoperative delirium ($P = 0.01$) (8). Siripoonyothai and Sindhvananda found that ketamine infusion at a dose of 1 mg/kg/h during CPB reduced delirium incidence within 24 hours postoperatively ($P = 0.04$) (8).

Additionally, Wittwer et al. observed no significant difference in the incidence of delirium between patients administered ketamine at doses of 1-2 mg/kg and those receiving propofol ($P = 0.23$) (2). Similarly, a study on orthopedic surgery patients revealed no notable difference in postoperative mental status between those who received a ketamine bolus of 0.5 mg/kg and the

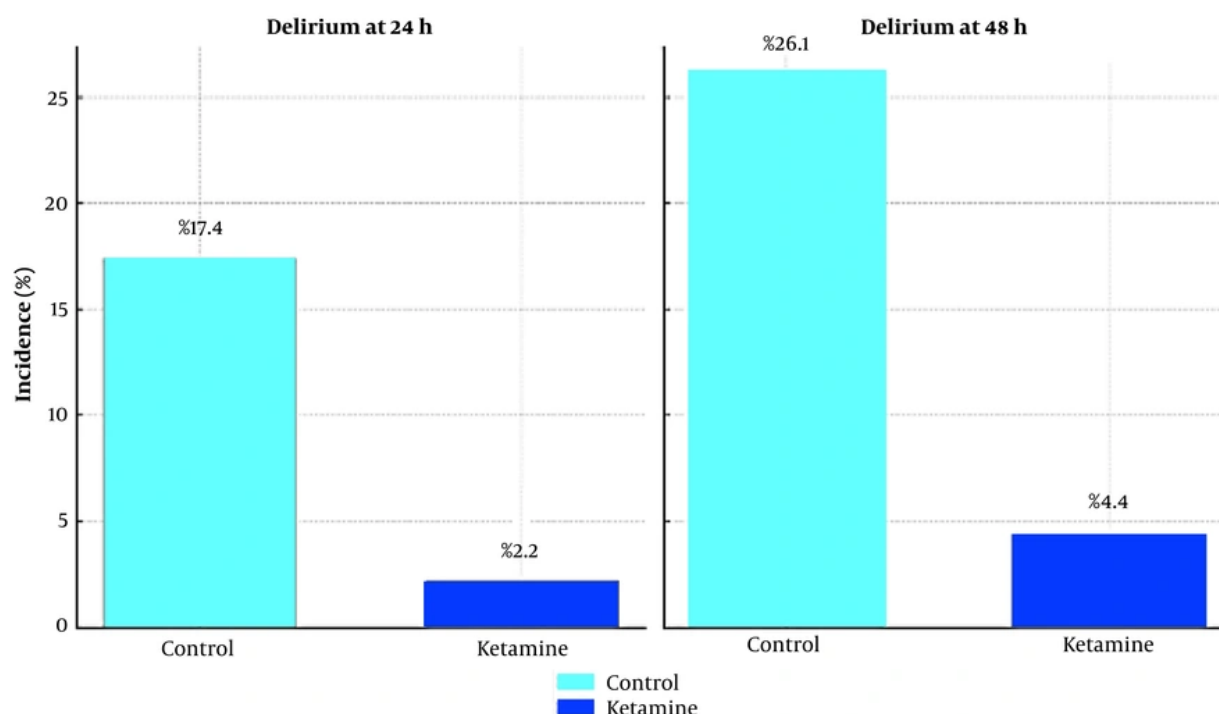


Figure 2. Incidence of postoperative delirium at 24 and 48 hours in ketamine and control groups

Table 2. Comparison of Delirium Incidence and Intraoperative Hemodynamic Parameters Between the Control and Ketamine Groups ^{a, b}

Parameters	Control (n = 46)	Ketamine (n = 46)	RR ^c	ARR ^c	NNT ^c	P-Value (Bonferroni Adjusted) ^d
Incidence of delirium at 24 h	8 (17.39)	1 (2.17)	0.13 (0.02 - 0.99)	15.22	6.58	0.022
Incidence of delirium at 48 h	12 (26.09)	2 (4.35)	0.17 (0.04 - 0.73)	21.74	4.61	0.019
MAP (mmHg)	97.99 ± 8.45	98.91 ± 9.13	-	-	-	0.635
Duration of surgery (min)	340.68 ± 29.24	344.18 ± 31.56	-	-	-	0.513
CPB time (min)	91.21 ± 15.67	89.11 ± 14.45	-	-	-	0.578
CC time (min)	54.12 ± 12.43	57.32 ± 13.26	-	-	-	0.412

Abbreviations: RR, relative risk; ARR, absolute risk reduction; NNT, number needed to treat; MAP, mean arterial pressure; CPB, cardiopulmonary bypass; CC, cross-clamp.

^a Values are expressed as No (%) or mean ± SD.

^b For continuous variables, simple mean comparisons were used based on independent-samples *t*-tests.

^c For categorical outcomes (delirium incidence), effect sizes are expressed as RR, ARR, and NNT with 95% confidence intervals.

^d P-values for delirium outcomes were adjusted using Bonferroni correction (alpha = 0.025).

placebo group (19). Cameron et al. also reported no difference in the incidence of delirium between the ketamine and placebo groups in a cohort of 80 patients undergoing CABG surgery ($P = 0.28$) (20).

Notably, our findings contrast with those of several large, high-quality studies reporting no benefit of

ketamine in the prevention of postoperative delirium. In a multicentre randomized controlled trial involving 672 patients undergoing major cardiac and non-cardiac surgery, Avidan et al. found that intraoperative ketamine administration (0.5 mg/kg bolus followed by infusion) did not reduce the incidence of delirium

Table 3. Intraoperative Parameters by Delirium Status ^{a,b,c}

Parameters	Non-delirious (n = 82)	Delirious (n = 10)	P-Value	Mean Difference (95%CI)	Statistical Test
Duration of Surgery (min)	328.85 ± 28.13	352.50 ± 30.74	0.530	23.65 (-3.20 to 50.50)	Independent t-test (Welch)
CPB Time (min)	98.08 ± 12.24	84.33 ± 13.67	0.440	-13.75 (-22.70 to -4.80)	Independent t-test (Welch)
CC Time (min)	60.13 ± 11.28	48.67 ± 9.22	0.371	-11.46 (-19.90 to -3.00)	Independent t-test (Welch)
Ejection Fraction (%)	49.65 ± 3.85	43.75 ± 4.29	0.368	-5.90 (-8.50 to -3.30)	Independent t-test (Welch)

Abbreviations: CPB, cardiopulmonary bypass time; CC, cross-clamp time.

^a Values are expressed as mean ± SD unless indicated.

^b Comparisons between delirious and non-delirious groups were conducted using the independent samples t-test with Welch's correction when variances were unequal. Mean differences represent Delirious-Non-delirious. The small sample size in the delirious group (n = 10) limits the precision and statistical power of comparisons.

^c Comparisons are exploratory and underpowered (n = 10 delirious patients); results should be interpreted cautiously.

compared with placebo (16). Similarly, Hovaguimian et al., in a systematic review and meta-analysis of 16 randomized controlled trials, concluded that ketamine had no significant effect on postoperative delirium prevention (14). The discrepancies between these neutral findings and our results may be explained by several methodological and clinical differences across studies, including heterogeneity in patient populations (mixed surgical cohorts versus isolated CABG procedures), ketamine dosing strategies, timing and duration of administration, and the delirium assessment instruments used. Importantly, the length of postoperative follow-up may have played a critical role, as many of the negative studies assessed delirium beyond 48 hours, thereby capturing delayed-onset delirium that may not have been detected within the limited observation window of our study.

Additional differences can be observed when comparing our results with those of Wittwer et al. Several methodological factors may account for the divergent findings. First, the studies employed different delirium screening tools; Wittwer et al. used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), whereas we applied the ICDSC. Although both instruments are validated, they differ in sensitivity and diagnostic thresholds, potentially influencing delirium detection rates. Second, the study populations varied substantially. Wittwer et al. included elderly patients (≥ 70 years) undergoing complex cardiac surgeries, such as multivalve procedures and redo sternotomies, while our trial was restricted to patients undergoing isolated CABG with a wider age range (40 - 80 years) (2). Differences in age, surgical complexity, and baseline vulnerability to delirium may therefore have contributed to the observed outcome variability. Furthermore, the comparator interventions were not equivalent, as ketamine was compared with propofol in Wittwer et al.'s study (2), whereas our trial employed a placebo control during anesthesia

induction. Variations in ketamine dosing and anesthetic protocols may have further influenced the results.

Taken together, these differences in study design, patient characteristics, assessment methodologies, and follow-up duration underscore the inherent complexity of delirium research. Given the conflicting evidence in the current literature, our findings should be interpreted cautiously and considered hypothesis-generating rather than definitive. Confirmation in larger, multicentre trials with standardized delirium assessment tools and extended postoperative follow-up is warranted before ketamine can be recommended as a routine strategy for delirium prevention in patients undergoing CABG surgery.

In our triple-blind randomized clinical trial, we examined the effect of intravenous ketamine on the incidence of postoperative delirium in patients undergoing CABG surgery. The results show that administering ketamine at a dose of 0.5 mg/kg significantly reduces the occurrence of delirium at both 24 and 48 hours following surgery in this patient group.

Our findings suggest that a single intraoperative dose of ketamine (0.5 mg/kg) may be associated with a reduced incidence of early postoperative delirium in patients undergoing CABG, potentially offering a simple and low-cost intervention within the anesthetic protocol for this high-risk population. If confirmed, such an effect could have downstream implications for ICU resource utilization and associated healthcare costs, although these secondary outcomes were not formally assessed in our study.

It is important to note, however, that the observed effect is based on a small number of delirium events — particularly only two cases in the ketamine group — and was limited to a 48 hour observation window, which may not capture delayed-onset delirium, the peak incidence of which often occurs beyond this timeframe. Furthermore, we did not systematically collect data on

ketamine-related adverse effects (e.g., emergence phenomena, hemodynamic instability), limiting our ability to conduct a comprehensive risk-benefit assessment.

While our results contribute to the ongoing discussion on pharmacological strategies for delirium prevention, they should be interpreted as preliminary. The absence of biomarker, neuroimaging, or long-term cognitive assessments precludes any inference regarding neuroprotection or lasting neurological benefits. Rather than indicating a definitive therapeutic role, our findings support the need for larger, rigorously designed trials that include extended follow-up, standardized delirium screening, and thorough safety monitoring. Such studies are necessary before ketamine can be recommended as a routine adjunct in the perioperative care of CABG patients.

5.1. Limitations

A limitation of our study was its single-center design, which may limit the generalizability of the findings to other institutions and populations. Additionally, due to time constraints, this study focused only on delirium incidence at 24 and 48 hours post-surgery, without examining the long-term effects of ketamine on delirium or other postoperative complications. Our 48 hour follow-up may have missed delayed-onset delirium, potentially underestimating true incidence. Moreover, the absence of systematic adverse event monitoring prevents a comprehensive risk-benefit assessment of ketamine in this context. Although our age range (40 - 80 years) reflects the typical demographic undergoing CABG in our clinical setting, the relative underrepresentation of older adults – particularly those over 80, who are at highest risk for delirium – may limit the applicability of our findings to more elderly populations. Convenience sampling may further limit the generalizability of our findings, and we did not assess long-term cognitive outcomes after hospital discharge. Furthermore, the exclusion of patients with psychiatric disorders, cerebrovascular disease, or high BMI limits the applicability of our results to many real-world CABG patients who commonly present with these comorbidities. Future studies are recommended to be conducted on larger and more diverse populations, including patients with various comorbidities and demographic differences, to enhance the generalizability of the results and gain a better understanding of ketamine's effects in different groups.

5.2. Conclusions

This study suggests that a single intravenous dose of ketamine (0.5 mg/kg) administered during anesthetic induction may be associated with a lower incidence of early postoperative delirium in patients undergoing cardiac surgery, with reduced rates observed at both 24 and 48 hours postoperatively. However, the small number of delirium events – particularly only two cases in the ketamine group – substantially limits the strength and precision of these findings. Additionally, the 48 hour follow-up window may have missed delayed-onset delirium, potentially underestimating the true incidence. While these preliminary results support further exploration of ketamine's role in delirium prevention, they should be interpreted with caution. Larger, multicenter randomized trials with extended follow-up periods, standardized delirium assessment protocols, and comprehensive monitoring of ketamine-related adverse effects are essential before any recommendations for clinical implementation can be made. This study contributes to ongoing efforts to identify effective strategies for mitigating postoperative delirium, a common and serious complication in surgical populations.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: M. M. K. and M. A. conceived the study idea, designed the research protocol, and supervised project implementation. M. M. K. contributed to methodology development, data quality control, and interpretation of clinical findings. S. S. carried out data collection, performed statistical analysis, and drafted the initial manuscript. M. R. M. D. provided clinical supervision, contributed to patient recruitment, and reviewed the manuscript critically for important intellectual content. A. M. assisted in study design, analysis validation, and manuscript revision. M. G. contributed to data collection, patient assessment, and administrative support. R. R. assisted in data management, literature review, and preparation of tables and figures. All authors read and approved the final manuscript.

Clinical Trial Registration Code:
[IRCT20231021059795N1](https://www.clinicaltrials.gov/ct2/show/study?term=IRCT20231021059795N1&rank=1).

Conflict of Interests Statement: The authors declare that there is no conflict of interest related to this study.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: This study was approved by our institutional ethics committee (IR.IUMS.REC.1402.833).

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Informed Consent: Prior to enrollment, informed consent was obtained from all participants.

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