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ORIGINAL ARTICLE

EFFECT OF A SUBANESTHETIC DOSE OF KETAMINE ON AWAKENING AND POSTOPERATIVE DEPRESSION AND ANXIETY IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFT SURGERY

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The present study was performed to evaluate the effect of subanesthetic dosage of ketamine on awakening and anxiety and depression status among patients undergoing coronary bypass graft (CABG) surgery. In this quasi-experimental study, 50 patients scheduled for elective CABG in a tertiary referral hospital were enrolled. Participants were allocated to the ketamine and control groups. In the ketamine group, infusion began immediately after induction of anesthesia and before skin incision, at 0.375 µg/kg/min, and was discontinued at skin closure. The control group received the equivalent volume of normal saline over the same time frame. Hemodynamic parameters [mean arterial pressure (MAP), heart rate (HR)] were recorded at baseline (before anesthesia induction), after induction but before skin incision, and upon arrival in the intensive care unit ICU. Preoperative and postoperative anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), with postoperative assessment performed 24 hours after extubation to ensure valid cognitive function. Sedation was assessed using the Ramsay Sedation Scale. The ketamine group showed a significantly higher proportion of awake patients at two hours post-operation (80% vs. 42.5%, $p = 0.034$) and faster recovery of consciousness over time ($\chi^2(3) = 11.18$, $p = 0.011$). Ketamine was associated with significantly lower anxiety (mean difference: -1.64, $p < 0.001$) and depression scores (mean difference: -1.52, $p < 0.001$) compared to the control group. A subanesthetic ketamine infusion, initiated after induction and continued until skin closure, significantly improved postoperative recovery in patients undergoing CABG surgery by promoting early awakening and reducing anxiety and depression scores 24 hours after the operation. These results highlight the potential of ketamine as an effective adjunct in perioperative care, warranting further investigation into its broader applications and long-term effects on patient outcomes.

Keywords: anxiety, awakening, cardiac surgery, depression, ketamine

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INTRODUCTION

Coronary artery bypass graft (CABG) surgery is associated with significant postoperative pain, anxiety, and depressive symptoms, which can negatively affect recovery even in patients without diagnosed psychiatric disorders (1,2). In cardiovascular surgery, there is a need for effective, opioid-sparing analgesia regimens that can provide maximal pain relief with minimal adverse effects (3). As an NMDA receptor antagonist with sedative, anxiolytic, and analgesic effects, ketamine represents a useful adjunct in perioperative pain management (4,5). Beyond its analgesic and mood-enhancing properties, ketamine exhibits significant anti-inflammatory and neuroprotective effects, including the modulation of pro-inflammatory cytokines, attenuation of ischemia–reperfusion injury, and reduction in the risk of postoperative delirium (6,7). These mechanisms are particularly relevant in the context of CABG surgery and cardiopulmonary bypass, highlighting ketamine's value as a multifaceted adjunct in perioperative care (8).

The impact of ketamine on mood and postoperative depression among surgical patients remains unclear, with conflicting findings in the literature. Some studies have reported improved mood and lower depression scores in patients receiving ketamine (9), while others have not found a significant difference between ketamine and control groups (10). These inconsistent results may be due to differences in surgical populations, dosing regimens, and outcome measures.

Several mechanisms have been proposed to explain the analgesic effects of ketamine, including modulation of pain signal transduction and interactions with muscarinic, serotonergic, opioid, and sodium channel receptors (11,12). Ketamine is often used in combination with opioids and benzodiazepines to provide a comprehensive approach to perioperative pain management (13,14). Additionally, ketamine demonstrated protective effects against local and generalized cerebral ischemia, trauma, postoperative cognitive dysfunction, and apoptosis in preclinical and clinical studies (15-18).

Despite these potential benefits, the widespread use of ketamine as an anesthetic and sedative agent was limited by concerns over the emergence of delirium and unpleasant psychotropic effects (19,20). The present study aimed to evaluate the impact of a subanesthetic dose of ketamine on awakening, postoperative depression, and postoperative anxiety in patients undergoing CABG surgery.

METHODS

In a quasi-experimental study, a total of 50 patients who were scheduled for elective coronary artery bypass graft (CABG) surgery in a referral hospital were evaluated. The inclusion criteria were age between 18 and 70 years and an ejection fraction greater than 35%. Patients were excluded if they had pulmonary, renal, or hepatic abnormalities, a history of neurological disorders, stroke, preoperative cognitive disorders, severe opioid addiction, uncontrolled diabetes, or uncontrolled hypertension.

At the beginning of the study, participants underwent neurological tests and completed the Hospital Anxiety and Depression Scale (HADS) to assess their preoperative anxiety and depression levels. The HADS is a well-validated, 14-item questionnaire comprising seven questions each for anxiety (HADS-A) and depression (HADS-D), and has been used in various clinical settings. Higher scores indicate greater levels of anxiety or depression (21-23). Preoperative hemodynamic parameters, including heart rate (HR), systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP), were also measured using standard techniques. Anesthesia induction was performed using midazolam (0.05 - 0.15 mg/kg), sufentanil (0.25 - 2 µg/kg), and propofol (1 - 2.5 mg/kg), followed by atracurium (0.15 - 0.2 mg/kg). Anesthesia was maintained with atracurium (1 - 2 µg/kg/min), propofol (50 - 150 µg/kg/min), and sufentanil (0.5 - 1.5 µg/kg/hour). Participants were allocated to the ketamine group or the control group. In the ketamine group, infusion began immediately after induction of anesthesia and before skin incision, at 0.375 µg/kg/min, and was discontinued at skin closure. The control group received the equivalent volume of normal saline over the same time frame. Bispectral index (BIS) monitoring was performed during the anesthesia maintenance phase until patients were transferred to the Intensive Care Unit (ICU).

Hemodynamic parameters (MAP, HR), arterial blood gas analysis, electrocardiogram (ECG), central venous pressure, and pulse oximetry were monitored at regular intervals, but MAP and HR were recorded at baseline (before anesthesia induction), after induction but before skin incision, and upon arrival in the ICU. The primary outcomes were awaking status (assessed using the RAMSAY sedation scale), postoperative anxiety, and depression (evaluated using the HADS). Preoperative HADS was evaluated during the pre-anesthesia clinic visit. Postoperative HADS was evaluated 24 hours postoperatively, when patients were fully awake and

oriented, to ensure validity. Also, operation time, intubation time, and length of hospital stay were evaluated.

Ethical considerations

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Prior to the initiation of the study, the protocol received approval from the Research Ethics Committee of Iran University of Medical Sciences (Ethical Code: IR.RHC.REC.1400.039). All participants were fully informed about the nature, purpose, and potential risks of the study. They provided written informed consent, ensuring that participation was voluntary and that they had the right to withdraw at any time without any effect on their medical care. Additionally, subanesthetic doses of ketamine were administered with careful attention to minimize potential adverse effects. Continuous monitoring of participants was implemented to ensure their safety and well-being during the study period. The research team remained committed to ethical standards throughout the study, with a focus on minimizing harm and maximizing benefits for all participants involved.

Statistical analysis

The study data were entered into SPSS version 24.0 for analysis. Quantitative variables were presented as mean ± standard deviation, and qualitative variables were presented as frequency and percentage. Independent sample t-test and Chi-square tests were used to analyze the differences in quantitative and qualitative variables between the ketamine and control groups, respectively. Primary outcomes, including awaking status, anxiety, and depression scores, were analyzed with a mixed-effects model to account for repeated measures. Mean differences and 95% confidence intervals (CIs) were reported. One-way analysis of variance (ANOVA) confirmed group differences in anxiety and depression scores, with significance set at $p < 0.05$. Awakening status was evaluated using ANOVA to compare the proportions of awake patients at 2 and 4 hours, and a Chi-square test for trend was used to analyze awakening patterns over time. Mediation analysis assessed the indirect effects of ketamine on anxiety and depression, utilizing bootstrapping to derive 95% confidence intervals (CIs). Where applicable, post hoc Bonferroni tests were conducted. All tests were two-tailed, with a significance threshold set at $p < 0.05$.

RESULTS

A total of 50 patients (32 male, 18 female) were included in the final analysis, with an equal male-to-female ratio (16/9) in both the ketamine and control groups. The mean age was similar between the ketamine and control groups (58.60 ± 4.78 vs. 58.32 ± 5.30 years, respectively; $p = 0.85$). Table 1 compares hemodynamic and operation-related parameters between the groups. The results indicate that there were no significant differences in intubation time, operation time, or hospitalization stay. HR during the first and second measurements was similar between groups. However, the third HR measurement showed a significant difference, with the ketamine group exhibiting lower values. Regarding MAP, there were no significant differences in the first and third measurements. However, a significant difference was observed in the second MAP measurement, with the ketamine group showing higher values.

Table 1. *Comparing hemodynamic and operation-related parameters between the ketamine and control groups*

Variables	Control group (n = 25)	Ketamine group (n = 25)	p-value
Intubation time (hours)	13.16 ± 2.44	12.92 ± 2.86	0.75
Operation time (min)	188.80 ± 31.67	202.80 ± 33.01	0.31
Hospitalization Stay	55.60 ± 6.26	53.80 ± 6.27	0.31
First HR	89.56 ± 10.66	83.84 ± 14.65	0.12
Second HR	69.0 ± 9.22	66.16 ± 8.18	0.26
Third HR	82.60 ± 7.05	77.48 ± 9.15	0.03
First MAP	98.28 ± 10.61	92.64 ± 13.32	0.11
Second MAP	60.16 ± 6.75	75.40 ± 12.99	< 0.00
Third MAP	73.76 ± 8.07	77.04 ± 13.40	0.2

As presented in Table 2, initial assessments (pre-intervention) revealed no statistically significant differences in the mean scores for anxiety (HADS-A) or depression (HADS-D) between the control group and the ketamine group ($p > 0.05$), confirming baseline homogenity between the groups. Following the intervention, statistically significant differences were observed between the two groups. Anxiety (HADS-A) and depression (HADS-D) scores were significantly reduced in the ketamine group compared to the control group ($p < 0.001$).

Table 2. *HADS scores for anxiety and depression in the ketamine and control groups*

Variables	Time-point	Control Group (Mean ± SD)	Ketamine Group (Mean ± SD)	p-value*
Anxiety (HADS-A)	Pre-intervention	8.6 ± 1.2	8.4 ± 1.3	0.412
	Post-intervention	8.2 ± 1.3	6.8 ± 1.1	< 0.001
Depression (HADS-D)	Pre-intervention	7.9 ± 1.4	7.8 ± 1.5	0.776
	Post-intervention	7.3 ± 1.5	6.1 ± 1.2	< 0.001

As presented in Table 3, patients in the ketamine group were more likely to be awake at the 2-hour assessment compared to the control group (80% vs. 42.5%, respectively; $p = 0.034$). However, by the 4-hour assessment, the difference in the proportion of awake patients between the two groups was no longer statistically significant (72% in the ketamine group vs. 52% in the control group; $p = 0.145$). At the 6-hour and 8-hour assessments, the proportion of awake patients was similar between the ketamine and control groups (88% awake in both groups). To further analyze the temporal pattern of patient awakening, we conducted a Chi-square test for trend. This analysis revealed a significant difference in the proportion of awake patients over time between the ketamine and control groups ($\chi^2(3) = 11.18$, $p = 0.011$), indicating that the ketamine group had a faster recovery of consciousness compared to the control group.

Table 3. *Comparing frequency of awaking status of patients among ketamine and control groups*

Variables	Awaking status	Control group (n = 25)	Ketamine group (n = 25)	p-value
Two hours after the operation	Awake	17 (68%)	23 (92%)	0.034
	Sleep	8 (32%)	2 (8%)	
Four hours after the operation	Awake	13 (52%)	18 (72%)	0.145
	Sleep	12 (48%)	7 (28%)	
Six hours after the operation	Awake	22 (88%)	22 (88%)	-
	Sleep	3 (12%)	3 (12%)	
Eight hours after the operation	Awake	25 (100%)	25 (100%)	-
	Sleep	-	-	

The mixed-effects model analysis revealed that patients in the ketamine group had significantly lower anxiety scores compared to the control group (mean difference: -1.64, 95% CI: -2.05 to -1.23; $p < 0.001$). Similarly, patients in the ketamine group had significantly lower depression scores compared to the control group (mean difference: -1.52, 95% CI: -1.90 to -1.14; $p < 0.001$). These effects were consistent across the subgroup analyses, and there were no significant interactions between group and the potential effect modifiers (age, sex, or surgical complexity). To further confirm these findings, we performed ANOVA tests for awakening status, anxiety, and depression outcomes (Table 4). The between-group ANOVA for postoperative anxiety (HADS) showed a statistically significant difference between the ketamine and control groups, $F(1, 48) = 31.79$, $p < 0.001$. Similarly, the between-group ANOVA for postoperative depression (HADS) revealed a statistically significant difference between the

two groups, F(1, 48) = 24.83, p < 0.001. Additionally, the between-group ANOVA for the 2-hour assessment of awakening status (Ramsay Sedation Scale) indicated a statistically significant difference in the proportion of awake patients, F(1, 48) = 4.63, p = 0.026, while the difference was no longer significant at the 4-hour assessment, F(1, 48) = 2.17, p = 0.174.

The mediation analysis showed that the effect of ketamine on postoperative anxiety (indirect effect: -0.58, 95% CI: -1.06 to -0.19) and depression (indirect effect: -0.47, 95% CI: -0.90 to -0.15) was partially mediated by the differences in awakening status between the two groups.

Table 4. *ANOVA results for awakening status, anxiety, and depression scores*

Outcome	Time point	F-value	df	p-value	Post hoc Results (Bonferroni)
Awakening status	2 hours	4.63	1, 48	0.026	Ketamine > Control
	4 hours	2.17	1, 48	0.174	No significant difference
	6 hours	-	-	-	No significant difference (88% awake in both groups)
	8 hours	-	-	-	No significant difference (all patients awake)
Postoperative anxiety	24 hours post-op	31.79	1, 48	< 0.001	Ketamine < Control (Mean difference: -1.64)
Postoperative depression	24 hours post-op	24.83	1, 48	< 0.001	Ketamine < Control (Mean difference: -1.52)

DISCUSSION

In our study, we assessed the impact of subanesthetic dosage of ketamine on hemodynamic parameters, anxiety/depression status, and awakening of patients undergoing CABG. Study findings showed that hemodynamic parameters were similar between the two groups, and on the other hand, advising subanesthetic dosage of ketamine did not have adverse impacts on the hemodynamic situation of patients undergoing CABG. Patients in the ketamine group had experienced significantly lower anxiety and depression in comparison with patients in the control group. Moreover, subanesthetic dosage of ketamine had no adverse impacts on sedation and awakening of patients, and all of the study patients were awake eight hours after the operation.

Although anesthetics tried to provide a better situation for pain control during the postoperative period, more than two-thirds of patients reported that their pain control regimen was not adequate and they felt more pain during the postoperative period (24). More than anxiety, pain in the postoperative period can cause some complications, such as nausea, vomiting, delayed surgery recovery, and extended hospitalization (25). According to this challenge, anesthetists try to provide well-planned pain management protocols to reduce the pain experiences of patients and control other related complications such as postoperative anxiety and depression. Ketamine, as one of the NMDA agents was used for its analgesic properties during the postoperative period (22). Ketamine decreases pain by inhibiting glutamate, a neurotransmitter that binds to NMDA receptors and prevents pain transmission (26). Ketamine in subanesthetic dosage (less than 0.3 mg/kg) had analgesic and opioid-sparing effects and controlled hyperalgesia due to opioid consumption during the postoperative period (8, 26). Similar studies reported that subanesthetic dosage of ketamine is not associated with significant complications of high dosage of ketamine, such as an increase in the secretion of the respiratory system, delirium, and double vision (27).

Numerous studies have reported that, regardless of the treatment results, many patients still suffer from postoperative pain (28). Lahtinen et al. in their study reported that 49% of patients undergoing CABG experienced severe pain at rest, 78% while coughing, and 62% of patients experienced pain during movement (29). In another study, patients undergoing CABG had activity-related pain until the sixth day after the operation, and most of the pain was experienced while coughing and deep breathing (30).

For many years, ketamine has been used as a general anesthetic, and in recent years, its subanesthetic dosage has been used as analgesia in the postoperative period.

Ketamine, as a non-competitive antagonist of NMDA receptors, has been shown to inhibit opioid-induced analgesic tolerance and hyperalgesia (31,32). We have found few studies that use ketamine in cardiac surgery. In Nesher et al. study, patients who received ketamine had lower pain scores and morphine consumption (28). Other studies indicate that, beyond its analgesic properties, ketamine can reduce delirium after cardiopulmonary bypass and exert antidepressant effects. (33). Depression has been known as one of the main contributors of post-operative morbidity, and patients with underlying depression at baseline may be at an increased risk of postoperative complications (34). In a retrospective study by Elsamadicy, patients who had preoperative depression had twice the chance of developing postoperative delirium (35). Blumenthal et al., in their study, concluded that post-operative depression may occur in as high as 40% of patients undergoing coronary artery bypass grafting (CABG) procedures (36). In contrast, Aguayo et al. in their study reported that only 5.1% of patients may be at risk of developing post-operative depression following the CABG procedure (37). Regardless of the discrepancies in incidence, most of the similar studies focused on the implications of post-operative depression on patient outcomes (34-37).

While much of the literature emphasizes ketamine's analgesic properties, it is important to acknowledge that its clinical effects are likely multifactorial and extend beyond pain modulation. Ketamine has well-documented anti-inflammatory properties, which may contribute to its beneficial effects in the postoperative period. Ketamine reduces the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting the anti-inflammatory cytokines, such as interleukin-10 (IL-10) (38,39). These effects may mitigate the systemic inflammatory response commonly associated with surgery and anesthesia, potentially improving recovery outcomes. Reduced inflammation may also play a role in the observed improvements in mood, as inflammation is increasingly recognized as a contributor to depression and anxiety (6, 40). In addition, ketamine's neuroprotective properties may help explain its effects on postoperative recovery. Ketamine has been shown to modulate ischemia-reperfusion injury, a condition that can occur during surgery due to transient reductions in blood flow to tissues. By acting as an NMDA receptor antagonist, ketamine reduces excitotoxicity and calcium overload in neurons, thereby preventing cellular damage (7, 41). These neuroprotective effects may further contribute to improved cognitive recovery and mood stabilization in the early postoperative period.

According to the findings of our study, advice on subanesthetic dosage of ketamine can control anxiety and depression among study participants, so hopefully, the frequency of CABG postoperative complications will decrease. While ketamine led to higher arousal scores at the 2-hour postoperative assessment, the clinical significance of this finding may be limited as it did not result in measurable benefits such as shorter mechanical ventilation duration or reduced ICU stay. This suggests that the early awakening advantage observed might not independently influence long-term recovery metrics or overall clinical outcomes. Also, one of the most promising clinical implications of ketamine use in the perioperative setting is its potential to facilitate early extubation and expedite ICU discharge, contributing to fast-tracking protocols. However, this aspect was not evaluated in the present study. Future research should prioritize outcomes such as time to extubation, readiness for ICU transfer, hospital length of stay, or patient-reported functional recovery, and their impact on overall resource utilization and patient recovery. Including these endpoints in future protocols could provide critical insights into the broader applicability of ketamine in enhancing perioperative care efficiency.

In conclusion, it seems that sub-anesthetic dose of ketamine administration significantly enhances postoperative recovery by promoting a faster return to consciousness and reducing anxiety and depression in patients undergoing CABG surgery. The findings suggest that ketamine not only enhances early awakening status but also has a beneficial effect on psychological well-being following surgery. These results highlight the potential of ketamine as an effective adjunct in perioperative care, warranting further investigation into its broader applications and long-term effects on patient outcomes.

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Statement of Ethics

This study protocol was reviewed and approved by the

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Competing Interest

The authors declare no relevant conflicts of interest.

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