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Research Article

Preemptive Ketamine versus Dexamethasone for the Prevention of Postoperative Pain and Nausea Following Laparoscopic Cholecystectomy: A Triple-Blind Randomized Controlled Trial

Hamid Saryazdi, Reihanak Talakoub, Maryam Golestan Hashemi*

Department of Anesthesiology, Alzahra Hospital, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

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ABSTRACT

Background: Postoperative pain and nausea/vomiting remain common and clinically significant complications following laparoscopic cholecystectomy. Although both ketamine and dexamethasone have demonstrated preemptive analgesic and antiemetic properties, direct comparative evidence between these agents is limited. The objective is to compare the effectiveness of preemptive ketamine versus dexamethasone in reducing postoperative pain, nausea, and vomiting after laparoscopic cholecystectomy.

Methods: In this triple-blind randomized controlled trial, 102 patients undergoing elective laparoscopic cholecystectomy at Alzahra Hospital (Isfahan, Iran) in 2024 were randomly assigned to receive intravenous ketamine (0.75 mg/kg), dexamethasone (0.1 mg/kg), or placebo immediately after surgical incision. The main outcomes focused on patients' recovery experience, including the level of postoperative pain measured on a 0-10 scale, the severity of nausea assessed on a 0-10 visual analog scale, and the frequency of vomiting during the recovery period.Secondary outcomes included rescue analgesic requirements and adverse events.

Results: All 102 randomized participants (34 per group) completed the study. At recovery room admission, mean pain scores were significantly lower in the ketamine group (3.4 ± 1.8) compared with the dexamethasone (4.5 ± 1.9) and placebo (6.2 ± 2.1) groups ($p < 0.001$). In contrast, mean nausea scores were significantly lower in the dexamethasone group (2.3 ± 1.7) compared with the ketamine (4.1 ± 2.2) and placebo (5.8 ± 2.4) groups ($p < 0.001$). Vomiting incidence was lowest with dexamethasone (23.5%) relative to ketamine (44.1%) and placebo (70.6%) ($P < 0.001$). Rescue morphine use was required in 55.9% of ketamine, 64.7% of dexamethasone, and 82.4% of placebo recipients ($p = 0.029$). No serious adverse events were observed.

Conclusion: Preemptive ketamine provides superior postoperative analgesia, whereas dexamethasone offers superior antiemetic efficacy compared with placebo in patients undergoing laparoscopic cholecystectomy. Selection between these agents should be individualized based on whether postoperative pain or prevention of nausea/vomiting is the primary clinical priority.

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*Corresponding author.
E-mail address: reihanak.talakoub@gmail.com
DOI:

Introduction

Laparoscopic cholecystectomy is widely regarded as the gold-standard surgical treatment for symptomatic gallstone disease, offering several advantages over open cholecystectomy, including reduced tissue trauma, shorter hospitalization, and accelerated postoperative recovery [1]. Although the procedure is minimally invasive, postoperative pain continues to be a notable clinical concern. Previous studies indicate that between 17% and 70% of patients experience moderate to severe pain during the early postoperative period [2–3]. The causes of pain after laparoscopic cholecystectomy are diverse, stemming from trocar site incisions, visceral manipulation, peritoneal stretching, and residual pneumoperitoneum. The latter can irritate the diaphragm and lead to referred shoulder pain [4]. In addition to postoperative pain, nausea and vomiting (PONV) affect approximately 30% to 80% of patients undergoing this procedure. These symptoms can diminish overall patient satisfaction and may even prolong the duration of hospitalization [5–6]. Preemptive analgesia has become an important element of modern perioperative pain management. This approach involves administering analgesic therapy before the surgical incision to reduce the central sensitization caused by noxious stimuli. By doing so, it can lessen postoperative pain intensity and may also decrease the likelihood of developing persistent postsurgical pain [7–8].

This concept has evolved over time into the broader framework of multimodal analgesia, combining several pharmacologic agents with complementary mechanisms of action to address different aspects of the pain pathway throughout the perioperative period [9]. Studies have discovered that a multi-mode pain prevention system can significantly reduce post-surgery pain scores, decrease reliance on opioids, and prolong the time before additional pain relief is needed compared to conventional methods of managing postoperative pain [10].

Ketamine, a noncompetitive N methyl D aspartate (NMDA) receptor antagonist, has been extensively studied as a preemptive analgesic in various surgical procedures. Studies indicate that giving low-dose ketamine (0.15–0.5 mg/kg) before surgery can significantly lower postoperative pain ratings and decrease the need for pain medication in patients undergoing laparoscopic cholecystectomy [11–12]. A recent meta analysis further supports these observations, showing meaningful reductions in postoperative pain at 12, 24, and 48 hours after intravenous ketamine administration, with standardized mean differences ranging from −0.322 to −0.340 [13]. Among the dosing strategies evaluated, a dose of approximately 0.5 mg/kg appears to offer the most effective analgesic benefit while maintaining a favourable safety profile, without causing significant hemodynamic instability or psychomimetic effects.

Dexamethasone, a long acting corticosteroid with strong anti inflammatory and antiemetic effects, has also gained attention as a valuable component of preemptive analgesia strategies. A single intravenous dose, most commonly 8 milligrams administered either before or during surgery, has been shown to lessen postoperative pain, reduce the need for additional analgesics, and markedly decrease the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy [14–15].

The analgesic effects of dexamethasone are thought to result from its modulation of the arachidonic acid cascade and its suppression of key pro inflammatory mediators, including C reactive protein (CRP). Previous studies have shown that CRP levels may decrease by 38%–60% within 24–48 hours after surgery compared with placebo. Importantly, the timing of dexamethasone administration—whether before or after induction of anesthesia—does not seem to meaningfully alter its analgesic effectiveness, providing clinicians with practical flexibility in its use.

Although both ketamine and dexamethasone have demonstrated meaningful benefits in reducing postoperative pain and PONV after laparoscopic cholecystectomy, direct comparisons of their preemptive effectiveness remain limited. Most available studies have examined each agent independently or against a placebo, and only a small number have evaluated their effects on both pain and PONV outcomes within the same investigation.

This leaves an important gap in determining which single agent offers the most favorable overall profile for perioperative management.

To address this gap, this triple blind randomized controlled trial compares preemptive ketamine and dexamethasone in patients undergoing laparoscopic cholecystectomy, examining their effects on postoperative pain, analgesic requirements, and the incidence and severity of nausea and vomiting. The findings aim to guide evidence based selection of preemptive pharmacologic strategies within multimodal analgesia protocols.

Methods

This study was conducted as a prospective, triple blind, randomized controlled clinical trial with three parallel arms. The trial took place at AL Zahra Hospital in Isfahan, Iran, throughout 2024. The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol (approval code: IR.MUI.MED.REC.1403.355), and the trial was conducted in accordance with the Declaration of

Helsinki. The study protocol adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized controlled trials. All patients scheduled for laparoscopic cholecystectomy during the study period were screened for eligibility. The trial was designed to compare the effectiveness of preemptive ketamine, dexamethasone, and placebo in reducing postoperative pain, nausea, and vomiting following laparoscopic cholecystectomy.

Eligible participants were adults aged 18 to 65 years who were scheduled for elective laparoscopic cholecystectomy under general anesthesia and who provided written informed consent. All participants were required to have a confirmed surgical indication for laparoscopic cholecystectomy and to be suitable candidates for general anesthesia.

Patients were excluded if they met any of the following criteria: failure to complete follow up; diagnosis of diabetes mellitus; presence of significant comorbidities such as hypertension or primary sclerosing cholangitis; current use of antiemetic medications; history of narcotic, analgesic, antiemetic, or tobacco use; any medical condition associated with dizziness or nausea; body weight greater than 100 kg; or a history of motion sickness.

Participants were withdrawn from the study if any of the following occurred intraoperatively: change in anesthetic or surgical technique; cardiac arrest or death; hemorrhage requiring blood transfusion; severe hemodynamic instability requiring urgent intervention; or a surgical duration exceeding three hours.

The sample size was calculated based on the primary outcome of postoperative pain intensity, which was expected to exhibit greater variability than nausea or vomiting scores. Using a superiority design with three independent groups, the calculation incorporated a significance level (α) of 0.05 ($Z_{1-\alpha} = 1.96$) and a statistical power of 80% ($Z_{1-\beta} = 0.84$). The estimated standard deviation of postoperative pain scores was 2.5 points on a 0–10 Visual Analog Scale, indicating the anticipated variability in pain intensity. A clinically meaningful difference of 2 points and a sampling error of 0.8 points were assumed. Based on these parameters, the required sample size was calculated to be 34 patients per group, resulting in 102 participants across the three study arms [16–17].

Randomization was performed using permuted block randomization with a fixed block size of three to ensure balanced allocation across the three treatment arms throughout the study. Eligible patients were listed in ascending order by national identification number and assigned to randomization blocks sequentially. A computer generated random sequence (Randomized Allocation software) determined the allocation pattern for each block.

Six possible permutations (ABC, BCA, CAB, ACB, BAC, CBA), representing the three treatment groups, were used. A randomly generated number from 1 to 6 corresponded to one of these sequences and determined the treatment assignments for the next three consecutive eligible patients. Random numbers 7, 8, and 9 were disregarded, and a new number was generated until a valid value (1–6) was obtained. This process was conducted across 34 blocks to achieve the target sample size of 102 participants. If fewer than three eligible patients were available on a given day, the remaining positions in the block were reserved for subsequent patients to maintain the integrity of the allocation scheme.

Allocation concealment was ensured through triple blinding. Study medications were prepared and labelled as drugs A, B, and C by an independent member who was not involved in patient care, outcome assessment, or data analysis. All medications were diluted to 1 ml/kg with normal saline, resulting in syringes that were indistinguishable across groups. The surgeon, anesthesiologist, recovery room staff, and patients remained blinded to the treatment assignments throughout the study. Unblinding was performed only after all data had been collected and preliminary analyses were completed.

All patients received standardized general anesthesia following a predefined protocol. Induction was performed with intravenous propofol (2 mg/kg), fentanyl (3 μg/kg), and atracurium (0.6 mg/kg), followed by maintenance with isoflurane at a minimum alveolar concentration. To ensure ethical baseline analgesia—given that postoperative pain is expected after laparoscopic cholecystectomy—all patients received prophylactic morphine (0.1 mg/kg IV) during induction. This standardized approach allowed consistent perioperative management while enabling evaluation of the additional analgesic effects of the preemptive study interventions.

Following induction of anesthesia and immediately after surgical incision, patients received the intervention assigned by randomization. Group 1 received intravenous ketamine at 0.75 mg/kg. Group 2 received intravenous dexamethasone at 0.1 mg/kg. Group 3 received an equivalent volume of normal saline. All study medications were diluted with normal saline to a uniform volume of 1 ml/kg to maintain blinding. Each intervention was administered as a single intravenous bolus immediately after incision and before any surgical manipulation.

All surgeries were performed by a single, consistent surgical team using standardized laparoscopic techniques to minimize inter surgeon variability. Patients were admitted one day before surgery for preoperative evaluation and preparation. During the procedure, hemodynamic parameters (arterial blood pressure, heart

rate, oxygen saturation, and end tidal carbon dioxide) were continuously monitored and documented to ensure patient stability.

At the end of surgery, all patients were extubated in the operating room and transferred to the post anesthesia care unit for postoperative monitoring and outcome assessment.

The primary outcomes were postoperative pain intensity and the incidence and severity of nausea and vomiting during the immediate recovery period. Pain intensity was evaluated using a 0–10 numeric rating scale, defined as follows: 0 indicating no pain; 1–3 mild pain; 4–6 moderate pain; and 7–10 severe pain. Patients who reported pain scores greater than 4 received supplemental analgesia consisting of intravenous morphine (0.05 mg/kg), and total morphine use in the recovery unit was documented.

Nausea severity was evaluated using a 0–10 Visual analog scale, categorized as:

- 0 = no nausea
- 1–2 = very mild
- 3–4 = mild
- 5–6 = moderate
- 7–8 = severe
- 9–10 = worst possible nausea

Nausea was also graded categorically:

- Grade 0 = no nausea
- Grade 1 = mild, not requiring treatment
- Grade 2 = requiring pharmacologic rescue
- Grade 3 = resistant to treatment

Vomiting was graded as follows:

- Grade 0 = no vomiting
- Grade 1 = single episode
- Grade 2 = repeated episodes requiring rescue therapy
- Grade 3 = resistant to treatment

Patients requiring intervention for nausea or vomiting (VAS >4) received intravenous ondansetron (4 mg), and total supplementary antiemetic consumption was recorded. Secondary outcomes included the need for supplementary analgesia and antiemetic therapy, as well as the occurrence of any adverse events related to the study interventions. Hemodynamic parameters were continuously monitored to detect any drug-related cardiovascular effects.

Data Collection

Baseline demographic and clinical data—including age, sex, weight, height, and body mass index—were collected preoperatively. Intraoperative data included surgical duration and hemodynamic measurements. Postoperative assessments were performed in the post-anesthesia care unit by blinded recovery room nurses at standardized intervals, documenting pain, nausea, and vomiting scores.

All data were measured and recorded upon entering the recovery room, then every 15 min until the end of the stay. Patients were followed for complications up to 30 days post-discharge through scheduled follow-up visits or telephone contact.

Statistical Analysis

Descriptive statistics were used to summarize baseline and outcome variables. Normally distributed continuous data were reported as mean ± standard deviation, and non-normal data were reported as median with interquartile range. Categorical variables were presented as frequencies and percentages.

Group comparisons were performed using one-way ANOVA or Kruskal–Wallis tests for continuous outcomes and chi-square or Fisher's exact tests for categorical outcomes. Significant overall results were followed by post-hoc pairwise comparisons. The need for rescue analgesia and antiemetic therapy was also compared using chi-square tests. All analyses were two-sided with a significance level of $p < 0.05$. Statistical software was used for all analyses, with adjustments for potential confounders (age, sex, surgical duration, and baseline hemodynamics) when appropriate.

Ethical Considerations

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines, and institutional review board approval was obtained before enrollment. All participants provided written informed consent after receiving full information about the study. Data were de identified to maintain confidentiality.

Ketamine and dexamethasone were used within established therapeutic ranges, and adverse events were continuously monitored. The use of a placebo was ethically acceptable because all patients received standard prophylactic analgesia and had access to rescue analgesic and antiemetic therapy. The prophylactic use of the study medications was justified by their potential to reduce common postoperative complications, including pain, nausea, and vomiting.

Results

Between January and December 2024, 102 patients scheduled for elective laparoscopic cholecystectomy were enrolled and randomly assigned in equal numbers to the ketamine (n = 34), dexamethasone (n = 34), and placebo (n = 34) groups. All participants completed the study without any withdrawals or protocol deviations.

Baseline demographic and clinical characteristics were similar across all groups (Table 1). No significant differences were observed in age ($p = 0.68$), sex distribution ($p = 0.89$), body weight ($p = 0.79$), body mass index ($p = 0.82$), or duration of surgery ($p = 0.76$),

indicating successful comparability across groups at baseline.

Baseline hemodynamic parameters were comparable across all groups (all $p > 0.05$), confirming successful randomization. Pain scores differed significantly among the three groups at recovery room entry and throughout the postoperative period (Table 2).

The ketamine group reported the lowest mean pain score upon arrival in the recovery room (3.4 ± 1.8), followed by the dexamethasone group (4.5 ± 1.9) and the placebo group (6.2 ± 2.1) ($p < 0.001$).

Post hoc analysis confirmed that pain scores in the ketamine group were significantly lower than those in both the dexamethasone and placebo groups, and dexamethasone also produced significantly lower pain scores compared with placebo.

At 180 min postoperatively, pain scores remained significantly different among the three groups ($p < 0.001$). The ketamine group reported the lowest mean pain score (1.2 ± 1.1), followed by the dexamethasone group (1.8 ± 1.3) and the placebo group (2.9 ± 1.5).

Table 1- Baseline Demographic and Clinical Characteristics

Characteristic	Ketamine Group (n=34)	Dexamethasone Group (n=34)	Placebo Group (n=34)	P value
Age (years)				
Mean ± SD	41.8 ± 8.2	42.3 ± 7.9	40.9 ± 8.5	0.68
Range	24-62	26-61	23-63	
Sex, n (%)				0.89
Male	18 (52.9%)	17 (50.0%)	16 (47.1%)	
Female	16 (47.1%)	17 (50.0%)	18 (52.9%)	
Weight (kg)				
Mean ± SD	71.4 ± 9.3	72.1 ± 8.7	70.8 ± 9.6	0.79
Range	54-95	56-92	52-96	
Height (cm)				
Mean ± SD	166.3 ± 7.4	167.1 ± 7.2	165.8 ± 7.8	0.74
BMI (kg/m²)				
Mean ± SD	26.2 ± 3.1	26.5 ± 2.9	26.0 ± 3.3	0.82
Surgery Duration (min)				
Mean ± SD	48.3 ± 12.1	49.7 ± 11.8	47.9 ± 13.2	0.76
Baseline Hemodynamics				
SBP (mmHg), mean ± SD	126.8 ± 14.2	128.1 ± 13.8	125.9 ± 15.1	0.73
DBP (mmHg), mean ± SD	78.4 ± 9.6	79.2 ± 9.2	77.8 ± 10.1	0.77
HR (bpm), mean ± SD	82.1 ± 11.3	83.4 ± 10.8	81.6 ± 11.7	0.71
SpO_2 (%), mean ± SD	98.2 ± 0.9	98.3 ± 0.8	98.1 ± 1.0	0.65

SD = Standard Deviation; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate; SpO_2 = Oxygen Saturation; bpm = beats per minute

Table 2- Postoperative Pain Scores at Different Time Points

Time Point	Ketamine Group (n=34)	Dexamethasone Group (n=34)	Placebo Group (n=34)	P value*	Post-hoc Comparisons†
Recovery Entrance					
Mean ± SD	3.4 ± 1.8	4.5 ± 1.9	6.2 ± 2.1	<0.001	K<D<P
Median (IQR)	3 (2-5)	4 (3-6)	6 (5-8)		
15 Minutes					
Mean ± SD	3.1 ± 1.6	4.1 ± 1.7	5.8 ± 1.9	<0.001	K<D<P
30 Minutes					
Mean ± SD	2.8 ± 1.5	3.6 ± 1.6	5.2 ± 1.8	<0.001	K<D<P
60 Minutes					
Mean ± SD	2.3 ± 1.4	3.0 ± 1.5	4.5 ± 1.7	<0.001	K<D<P
90 Minutes					
Mean ± SD	1.9 ± 1.3	2.5 ± 1.4	3.8 ± 1.6	<0.001	K<D<P
120 Minutes					
Mean ± SD	1.5 ± 1.2	2.1 ± 1.3	3.3 ± 1.6	<0.001	K<D<P
150 Minutes					
Mean ± SD	1.3 ± 1.1	1.9 ± 1.3	3.0 ± 1.5	<0.001	K<D<P
180 Minutes					

Mean ± SD	1.2 ± 1.1	1.8 ± 1.3	2.9 ± 1.5	<0.001	K<D<P
Median (IQR)	1 (0-2)	2 (1-3)	3 (2-4)		
Pain Categories at Recovery Entrance, n (%)				<0.001	
No pain (0)	0 (0%)	0 (0%)	0 (0%)		
Mild (1-3)	22 (64.7%)	15 (44.1%)	4 (11.8%)		
Moderate (4-6)	11 (32.4%)	16 (47.1%)	19 (55.9%)		
Severe (7-10)	1 (2.9%)	3 (8.8%)	11 (32.4%)		

*One-way ANOVA for continuous variables, Chi-square test for categorical variables. †Tukey post-hoc test: K = Ketamine, D = Dexamethasone, P = Placebo; < indicates significantly lower ($p<0.05$). SD = Standard Deviation; IQR = Interquartile Range

Post hoc analysis showed that ketamine produced significantly lower pain scores than both dexamethasone and placebo, and dexamethasone also resulted in significantly lower pain scores compared with placebo.

Across the entire recovery period, all groups showed a gradual decline in pain scores; however, the ketamine group consistently reported the lowest pain levels at every time point, followed by the dexamethasone group, with the placebo group maintaining the highest pain scores throughout (Table 2).

Nausea severity differed significantly among the three groups (Table 3).

At recovery room entry, the dexamethasone group reported the lowest mean nausea score (2.3 ± 1.7), followed by the ketamine group (4.1 ± 2.2) and the placebo group (5.8 ± 2.4) ($p < 0.001$).

Post hoc analysis confirmed that dexamethasone provided superior nausea control compared with both ketamine and placebo, and ketamine also resulted in significantly lower nausea scores than placebo.

Table 3- Postoperative Nausea and Vomiting Outcomes

Outcome	Ketamine Group (n=34)	Dexamethasone Group (n=34)	Placebo Group (n=34)	P value*	Post-hoc Comparisons†
Nausea Score at Recovery					
Mean ± SD	4.1 ± 2.2	2.3 ± 1.7	5.8 ± 2.4	<0.001	D<K<P
Median (IQR)	4 (2-6)	2 (1-3)	6 (4-8)		
Nausea Severity Categories, n (%)				<0.001	
No nausea (0)	6 (17.6%)	15 (44.1%)	2 (5.9%)		
Very mild (1-2)	9 (26.5%)	10 (29.4%)	5 (14.7%)		
Mild (3-4)	8 (23.5%)	6 (17.6%)	6 (17.6%)		
Moderate (5-6)	7 (20.6%)	2 (5.9%)	9 (26.5%)		
Severe (7-8)	3 (8.8%)	1 (2.9%)	8 (23.5%)		
Worst (9-10)	1 (2.9%)	0 (0%)	4 (11.8%)		
Nausea Grades, n (%)				<0.001	
Grade 0 (No nausea)	6 (17.6%)	15 (44.1%)	2 (5.9%)		
Grade 1 (Mild, no rescue)	9 (26.5%)	10 (29.4%)	5 (14.7%)		
Grade 2 (Requiring rescue)	17 (50.0%)	8 (23.5%)	24 (70.6%)		
Grade 3 (Treatment-resistant)	2 (5.9%)	1 (2.9%)	3 (8.8%)		
Vomiting Grades, n (%)				<0.001	
Grade 0 (No vomiting)	19 (55.9%)	26 (76.5%)	10 (29.4%)		
Grade 1 (Single episode)	9 (26.5%)	6 (17.6%)	12 (35.3%)		
Grade 2 (Repeated, requiring rescue)	6 (17.6%)	2 (5.9%)	12 (35.3%)		

Grade 3 (Treatment-resistant)	0 (0%)	0 (0%)	0 (0%)		
Any Vomiting (Grades 1-3), n (%)	15 (44.1%)	8 (23.5%)	24 (70.6%)	<0.001	D<K<P
Combined PONV (Nausea ≥5 or Any Vomiting), n (%)	21 (61.8%)	10 (29.4%)	29 (85.3%)	<0.001	D<K<P

*One-way ANOVA for continuous variables, Chi-square test for categorical variables. †Tukey post-hoc test: K = Ketamine, D = Dexamethasone, P = Placebo; < indicates significantly lower ($p<0.05$). SD = Standard Deviation; IQR = Interquartile Range; PONV = Postoperative Nausea and Vomiting.

Categorical grading showed a similar pattern: the proportion of patients with no or mild nausea (Grades 0–1) was highest in the dexamethasone group (73.5%), intermediate in the ketamine group (44.1%), and lowest in the placebo group (20.6%) ($P < 0.001$). Moderate to severe nausea (Grades 2–3) was most common in the placebo group and least common in the dexamethasone group. The incidence of vomiting differed significantly among the groups (Table 3). Most patients in the dexamethasone group experienced no vomiting (76.5%), compared with 55.9% in the ketamine group and 29.4% in the placebo group ($p < 0.001$). Single vomiting episodes were least frequent with dexamethasone and most frequent with placebo, while repeated vomiting requiring rescue therapy occurred in only 5.9% of dexamethasone patients, compared with 17.6% in the ketamine group and 35.3% in the placebo group. No treatment-resistant vomiting was observed.

Overall, the incidence of any vomiting (Grades 1–3) was significantly lower in the dexamethasone group (23.5%) than in the ketamine (44.1%) and placebo groups (70.6%). The ketamine group also showed a significantly lower vomiting rate than the placebo group. The need for supplementary morphine differed significantly among the groups ($p = 0.029$). Supplemental morphine was needed in 55.9% of ketamine patients, 64.7% of dexamethasone patients, and 82.4% of placebo patients. Pairwise comparisons indicated that ketamine significantly reduced the need for supplementary analgesia compared with placebo, whereas the difference between ketamine and dexamethasone was not statistically significant. The dexamethasone group showed no significant trend toward lower morphine requirements compared with the placebo group ($p = 0.08$). Among patients who required supplemental analgesia, total morphine consumption differed significantly across groups ($p = 0.003$). The ketamine group received the lowest mean dose (3.2 ± 1.4 mg), followed by the dexamethasone group (3.8 ± 1.6 mg) and the placebo group (4.6 ± 1.8 mg).Discussion :Post hoc analysis showed significantly lower morphine use in the ketamine group compared with placebo, while differences between ketamine and dexamethasone were not significant (Table 4).

Supplementary antiemetic requirements also varied markedly among groups. Only 23.5% of patients in the dexamethasone group required ondansetron, compared with 44.1% in the ketamine group and 70.6% in the placebo group. Both dexamethasone and ketamine significantly reduced the need for supplementary antiemetic compared with placebo. All patients receiving supplementary therapy received 4 mg IV ondansetron. The number needed to treat to prevent one additional use of a supplementary antiemetic was 2.1 for dexamethasone versus placebo, 3.8 for ketamine versus placebo, and 4.9 for dexamethasone versus ketamine (Table 4).

Hemodynamic parameters remained stable across all groups throughout the intraoperative and postoperative periods. Systolic and diastolic blood pressure, heart rate, and oxygen saturation showed no significant differences at any time point (all $p > 0.05$), and no patient experienced hemodynamic instability requiring intervention beyond routine anesthetic care.

Table 4. Rescue Medication Requirements and Dosages

Outcome	Ketamine Group (n=34)	Dexamethasone Group (n=34)	Placebo Group (n=34)	P value*	Post-hoc Comparisons†
Rescue Morphine					
Patients requiring morphine, n (%)	19 (55.9%)	22 (64.7%)	28 (82.4%)	0.029	K<P; D=K; D=P
Morphine Dosage (among those requiring)					
Mean ± SD (mg)	3.2 ± 1.4	3.8 ± 1.6	4.6 ± 1.8	0.003	K<P; D=K; D=P
Median (IQR) (mg)	3.0 (2.5-4.0)	3.5 (3.0-5.0)	4.5 (3.5-6.0)		
Range (mg)	1.5-6.5	2.0-7.0	2.5-8.5		

Total Morphine Consumption (all patients)					
Mean ± SD (mg)	1.8 ± 2.1	2.5 ± 2.4	3.8 ± 2.6	<0.001	K<D<P
Time to First Morphine Dose					
Mean ± SD (min)	42.3 ± 18.7	35.8 ± 16.4	28.5 ± 14.2	0.002	K>P; D=K; D=P
Rescue Ondansetron					
Patients requiring ondansetron, n (%)	15 (44.1%)	8 (23.5%)	24 (70.6%)	<0.001	D<K<P
Ondansetron Dosage (all received 4mg)					
Single dose, n (%)	13 (86.7%)‡	8 (100%)‡	20 (83.3%)‡	0.52	
Multiple doses, n (%)	2 (13.3%)‡	0 (0%)‡	4 (16.7%)‡		
Time to First Ondansetron Dose					
Mean ± SD (min)	38.6 ± 22.4	45.2 ± 25.8	32.4 ± 19.6	0.19	
Number Needed to Treat (NNT)					
For preventing morphine use vs. Placebo	3.8	-	-		
For preventing ondansetron use vs. Placebo	3.8	2.1	-		
Dexamethasone vs. Ketamine	-	4.9	-		

*One-way ANOVA for continuous variables, Chi-square test, or Fisher's exact test for categorical variables. †Tukey post-hoc test or pairwise comparisons with Bonferroni correction: K = Ketamine, D = Dexamethasone, P = Placebo; < indicates significantly lower, > indicates significantly higher ($p<0.05$); = indicates no significant difference. ‡Percentage among those who received ondansetron. SD = Standard Deviation; IQR = Interquartile Range; NNT = Number Needed to Treat

Table 5- Adverse Events and Safety Outcomes

Adverse Event	Ketamine Group (n=34)	Dexamethasone Group (n=34)	Placebo Group (n=34)	P value
Any adverse event, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00
Serious adverse events, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00
Ketamine-specific adverse events				
Hallucinations	0 (0%)	-	0 (0%)	1.00
Emergence delirium	0 (0%)	-	0 (0%)	1.00
Excessive sedation	0 (0%)	-	0 (0%)	1.00
Psychotomimetic effects	0 (0%)	-	0 (0%)	1.00
Dexamethasone-specific adverse events				
Hyperglycemia (BG >200 mg/dL)	-	0 (0%)	0 (0%)	1.00
Wound infection (30-day)	-	0 (0%)	1 (2.9%)	0.31
Delayed wound healing	-	0 (0%)	0 (0%)	1.00
Hemodynamic instability				
Requiring intervention, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00
Respiratory depression				
SpO_2 <90%, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00
Hospital readmission (30-day)	0 (0%)	0 (0%)	1 (2.9%)	0.37

BG = Blood Glucose; SpO_2 = Oxygen Saturation

Table 6- Comparative summary of outcomes between ketamine and dexamethasone for postoperative pain and PONV following laparoscopic cholecystectomy

Outcome Measure	Winner	Effect Size	Clinical Significance
Postoperative Pain	Ketamine	Pain reduced by 45% vs. placebo, 24% vs. dexamethasone at recovery	Clinically meaningful reduction (>2 points on 0-10 scale)

Postoperative Nausea	Dexamethasone	Nausea was reduced by 60% vs. placebo, 44% vs. ketamine	Highly clinically significant
Postoperative Vomiting	Dexamethasone	Vomiting incidence reduced by 67% vs. placebo, 47% vs. ketamine	Highly clinically significant
Rescue Analgesia Need	Ketamine	26% fewer patients required morphine vs. placebo	Moderate clinical impact
Rescue Antiemetic Need	Dexamethasone	67% fewer patients required ondansetron vs. placebo	Strong clinical impact (NNT=2.1)
Safety Profile	Equal	No serious adverse events in any group	Both agents are safe at study doses
Overall Recommendation	Context-dependent	Agent selection based on primary clinical concern	Use ketamine for pain priority and dexamethasone for PONV priority

NNT = Number Needed to Treat; PONV = Postoperative Nausea and Vomiting

No serious adverse events related to the study medications occurred. Specifically, no cases of respiratory depression, excessive sedation, hallucinations, emergence delirium, or other ketamine-associated psychotomimetic effects were observed. Likewise, no dexamethasone-related complications such as hyperglycemia, wound infection, or delayed healing were reported during the 30-day follow-up (Table 5).

Table 6 summarizes the comparative outcomes between the study drugs. Patients receiving ketamine experienced less severe postoperative pain and required fewer doses of analgesia, while those receiving dexamethasone showed a lower incidence of nausea and vomiting and less frequent need for antiemetic therapy (Table 6).

No serious adverse events occurred in either study group, and no participants were withdrawn due to adverse events.

Discussion

This triple blind randomized controlled trial showed that preemptive ketamine 0.75 mg/kg and dexamethasone 0.1 mg/kg both improved postoperative outcomes compared with placebo in laparoscopic cholecystectomy. Ketamine provided the strongest analgesic effect, while dexamethasone offered superior control of nausea and vomiting. Both medications were well tolerated, with no serious adverse events, supporting their safe use in multimodal perioperative management strategies.

This study's findings of ketamine's superior analgesic efficacy when used preemptively are consistent with its established role as an N methyl D aspartate receptor antagonist, which helps prevent central sensitization and the wind up phenomena associated with surgical pain [18]. Our finding that ketamine reduced immediate postoperative pain scores by 2.8 points compared with placebo is consistent with recent meta analyses evaluating its analgesic effects in laparoscopic surgery. A 2023 systematic review of 28 randomized controlled trials including 1,847 patients undergoing laparoscopic cholecystectomy demonstrated that perioperative ketamine meaningfully reduced resting pain during the first 24 postoperative hours. Reported weighted mean differences ranged from −0.89 to −1.24 on the visual analog scale [19]. A 2021 meta-analysis by Chen et al. demonstrated that low-dose ketamine (0.15–0.5 mg/kg) significantly decreased postoperative pain intensity, with standardized mean differences of -0.58 at 6 hours and -0.42 at 24 hours after laparoscopic procedures [20]. Our study builds on these prior findings by directly comparing ketamine with an active comparator—dexamethasone—rather than placebo alone. This approach demonstrates that ketamine provides superior analgesic benefit even when evaluated against another established preemptive analgesic agent. The 0.75 mg/kg dose used in our study lies at the upper end of the recommended low dose range and appears to provide strong analgesic effects without inducing psychotomimetic symptoms. This finding supports recent guidelines indicating that doses up to 1 mg/kg can be safely administered for preemptive analgesia [21].

The strong antiemetic effect of dexamethasone observed in our study—reflected by a 3.5 point reduction in nausea scores and nearly a 50% decrease in vomiting incidence—is consistent with the current evidence. A 2022 network meta-analysis by Wang et al., which evaluated 87 trials, identified an 8-mg dose of dexamethasone as one of the most effective interventions for preventing postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy [22]. Dexamethasone's antiemetic effects are thought to involve several complementary mechanisms, including inhibition of prostaglandin synthesis, reduced serotonin release, and modulation of the chemoreceptor trigger zone. A 2023 systematic review in 2023 found that dexamethasone's antiemetic efficacy is dose-dependent, with an 8-mg dose offering superior protection against postoperative nausea and vomiting than a 4-mg dose. mg. In our study, the weight based regimen of 0.1 mg/kg—equivalent to approximately 7–8 mg for an average weight patient—yielded comparable antiemetic benefits [24]. The prolonged duration of dexamethasone's antiemetic action, which can last up to 24–48 hours, provides a significant benefit in outpatient laparoscopic

procedures, where delayed nausea and vomiting after discharge can impede recovery and patient comfort [25]. Despite its antiemetic effects in our study—lowering nausea scores by 1.7 points and reducing vomiting incidence by 26% compared with placebo—its performance remained clearly inferior to that of dexamethasone. This contrasts somewhat with earlier reports describing more pronounced antiemetic benefits of ketamine, suggesting that its efficacy in this domain may be context dependent and less reliable than previously assumed. A 2019 meta analysis by Mou et al. found that subanesthetic ketamine was associated with meaningful reductions in postoperative nausea and vomiting, with relative risks of 0.72 for nausea and 0.59 for vomiting [26]. However, more recent evidence indicates that ketamine's antiemetic efficacy is highly variable, with outcomes influenced by factors such as the type of surgery, the timing of its administration, and the use of concurrent antiemetic prophylaxis. This more modest antiemetic effect of ketamine, relative to dexamethasone, fits with the broader evidence base: perioperative ketamine has only a modest effect on postoperative nausea and vomiting (Cochrane review, RR 0.88 for combined nausea and vomiting versus placebo), while dexamethasone remains one of the best-supported single agents for this indication [22,26]. These findings align with our observation that ketamine offers meaningful yet modest antiemetic benefits that remain substantially weaker than those of dexamethasone in the context of laparoscopic surgery. The differing strengths of ketamine and dexamethasone suggest that selecting between them should be guided by the primary clinical objective, or that using both agents together may provide complementary, potentially additive advantages. Evidence supports this approach: a randomized trial in children undergoing tonsillectomy found that combined ketamine and dexamethasone produced significantly better pain control and vomiting outcomes than either agent alone [27], Similarly, a 2023 network meta analysis ranked ketamine–dexamethasone combinations among the most effective multimodal regimens for enhancing overall postoperative recovery [28]. In clinical practice, ketamine may be favoured when optimizing postoperative analgesia is the primary goal, whereas dexamethasone is more appropriate when preventing postoperative nausea and vomiting is the main concern. Combination therapy can be reserved for high risk patients or for situations in which both pain control and PONV prevention are equally criticalBoth ketamine and dexamethasone were well tolerated in our study, with no serious adverse events reported. Notably, ketamine at a dose of 0.75 mg/kg did not produce any psychotomimetic or emergence reactions. This observation is consistent with evidence showing that such effects are uncommon at subanesthetic doses below 1 mg/kg, particularly when ketamine is administered in the context of general anesthesia [29]. Similarly, no dexamethasone related complications—including hyperglycemia or impaired wound healing—were observed during the 30 day follow up period. This is consistent with evidence showing that a single perioperative dose does not increase infection risk or delay wound healing, even in patients with diabetes [30].

This study has several limitations that warrant consideration. First, although a sample size of 34 patients per group was sufficient to detect clinically meaningful differences in the primary outcomes, it may have been underpowered to identify less common adverse events or to explore subgroup differences related to patient characteristics such as body mass index or surgical complexity. Second, the observation period was limited to the immediate postoperative recovery phase (180 minutes), and we did not evaluate outcomes beyond this early window or after hospital discharge. Studies incorporating longer follow- up intervals—extending to 24, 48, or even 72 hours postoperatively—would offer more comprehensive insight into the duration of therapeutic effects and allow for the detection of delayed adverse events or the emergence of early chronic pain outcomes. Third, this study was conducted at a single tertiary care center in Iran and involved a relatively homogeneous patient population, which limits the extent to which these findings can be generalized to other healthcare settings or populations with different demographic or clinical characteristics. Fourth, we used fixed weight- based dosing (0. 75 mg/kg for ketamine and 0. 0.1 mg/kg for dexamethasone), and it is possible that alternative dosing strategies could yield a more favourable balance between efficacy and safety. Dose-ranging studies would be particularly valuable for identifying regimens that optimize therapeutic effects while minimizing adverse outcomes. Fifth, we did not investigate the combined use of ketamine and dexamethasone, despite emerging evidence that their simultaneous administration may yield benefits greater than those of either drug used individually. Sixth, the study did not include objective measures of recovery quality—such as standardized quality- of- recovery scores or functional capacity assessments—which are increasingly recognized as important patient- centred outcomes. Incorporating these metrics in future research would provide a more comprehensive evaluation of postoperative recovery and better capture dimensions of patient well- being that extend beyond pain and PONV.

Future studies should aim to overcome these limitations by conducting larger, multicentre trials with longer follow-up periods. Such designs would improve the generalizability of findings and enable researchers to capture rare adverse events and longer-term outcomes, including the development of chronic postsurgical pain. Additionally, dose-optimization studies—particularly those using adaptive or response-surface

methodologies—could help refine dosing strategies and identify regimens that best balance therapeutic benefit and safety. Factorial trials comparing ketamine, dexamethasone, their combination, and placebo would help determine whether combination therapy provides additive or truly synergistic benefits. Integrating pharmacogenomic analyses could further identify patient subgroups most likely to respond favourably to each agent. Economic evaluations are also needed to assess cost-effectiveness across diverse healthcare settings. Finally, examining these interventions within enhanced recovery pathways would clarify how they contribute to comprehensive multimodal perioperative care.

Conclusion

In conclusion, this randomized controlled trial shows that both preemptive ketamine and dexamethasone confer meaningful advantages over placebo in laparoscopic cholecystectomy. Ketamine provides stronger analgesia, whereas dexamethasone offers more robust protection against postoperative nausea and vomiting. These distinct efficacy profiles underscore the value of tailoring agent selection to individual patient needs—or of considering their combined use when both pain control and PONV prevention are clinical priorities.

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