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Research Article

Comparison of Ketamine and Opioids during Anesthesia for Reducing Postoperative Pain in Recovery in Patients Candidate for Laparoscopic Sleeve Gastrectomy Surgery: A Double-Blind, Randomized Clinical Trial

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Abstract

Introduction: Postoperative complications such as respiratory depression, nausea, and vomiting are particularly distressing for morbidly obese patients and pose significant challenges for anesthesiologists. This study aimed to evaluate the use of non-opioid analgesics to reduce opioid-related complications during recovery. We compared the analgesic effects of intravenous ketamine infusion and opioids in patients undergoing laparoscopic sleeve gastrectomy.

Methods: In this double-blind, randomized clinical trial, 66 morbidly obese patients (BMI ≥ 40 kg/m²) without significant comorbidities, referred to Baqiyatallah Hospital for laparoscopic sleeve gastrectomy from April 2022 to April 2023, were included. Patients were randomized into two groups of 33: the ketamine group received 0.5 mg/kg intravenous ketamine before positioning, followed by 0.5 mg/kg/hour infusion, while the opioid group received 10 mg intravenous morphine sulfate before positioning, followed by remifentanil infusion (0.25 µg/kg/minute) until the end of surgery.

Results: The mean morphine consumption during recovery was 2.3 mg in the ketamine group and 2.4 mg in the opioid group (p = 0.88). The mean VAS score during recovery was 3.725 in the ketamine group and 3.984 in the opioid group (p = 0.320). Propofol consumption was significantly lower in the opioid group (603.943 mg vs. 808.333 mg, p = 0.03). All patients in the ketamine group required trinitroglycerin (TNG) infusion for hemodynamic stability, compared to none in the opioid group. Hallucinations were significantly more frequent in the ketamine group (16.7% vs. 0%, p = 0.00).

Conclusion: In laparoscopic sleeve gastrectomy, ketamine and opioids showed no significant differences in pain scores, opioid consumption, or PONV incidence during recovery. However, propofol consumption was significantly lower in the opioid group, and hallucinations were more frequent in the ketamine group. These findings suggest that while ketamine may be a viable alternative to opioids, its side effects and higher propofol requirements warrant further investigation.

Keywords: Ketamine, Remifentanil, Morphine, Morbid Obesity, Sleeve Gastrectomy.

Introduction

Obesity has become one of the most significant global health challenges. In 2024, over one billion people worldwide are living with obesity, including approximately 880 million adults and 159 million children and adolescents [1]. Additionally, nearly three billion people are classified as overweight or obese. In 50 out of 53 European countries within the WHO, almost half of the population is overweight or obese. Regardless of ethnicity, gender, socioeconomic status, or geographic location, obesity rates have risen across all age groups globally. According to the WHO, the prevalence of overweight and obesity ranges from less than 20% in some countries to over 60% in others. Countries with the highest obesity rates are primarily high-income nations in North and South America, Europe, and Oceania [2-3].

In contrast, countries with the lowest obesity rates are predominantly located in sub-Saharan Africa and Southeast Asia. This disparity is striking; for example, the obesity prevalence in Japan is 3.7%, while in the United States, it is 38.2%. Countries with large populations, such as China and India, have a high absolute number of obese individuals. However, due to their vast populations, obesity is reported at only 5.7% and 5%, respectively. Furthermore, trends in obesity vary within countries. Over the past 20 years, obesity rates have steadily increased. In the 1980s, approximately 3% of men and 6% of women globally were obese, whereas by 2020, these figures had risen to 16% of women and 12% of men [1-3].

Legal approaches such as taxes on unhealthy foods, improved nutritional labeling, stricter definitions of portion sizes, bans on certain ingredients, and sodium consumption regulations have been implemented to address this crisis. However, significant gaps between scientific evidence and policy enforcement hinder the optimal effectiveness of these measures [1]. There is a consensus that bariatric surgery is currently the most effective and durable treatment for severe obesity. As a result, the number of bariatric surgeries performed has increased significantly in recent years. Several randomized clinical trials have demonstrated more significant weight loss and improvement in type 2 diabetes than non-surgical treatments within the first two years following bariatric surgery. Extensive observational studies have also shown long-term improvements in weight loss, diabetes, and lipid profiles with surgical methods [2].

Traditionally, postoperative pain management has relied heavily on opioids. While opioids provide immediate pain relief, they are associated with increased pain sensitivity upon discontinuation, PONV, higher postoperative opioid demand, respiratory depression, reduced gastrointestinal motility, urinary retention, endocrine disturbances, and weakened immune function [3].

Patients with obesity often experience various complications, including respiratory issues. Obesity is the most significant risk factor for obstructive sleep apnea-hypopnea syndrome (OSAHS). Approximately 70% of patients with OSAHS (up to 80% of men and 50% of women) are obese. Severe sleep apnea is more common in men and postmenopausal women, and there is a strong inverse correlation between the apnea-hypopnea index and arterial oxygen desaturation [4]. Consequently, the use of opioids in bariatric surgery is associated with further respiratory suppression and related complications.

Various studies have explored ketamine's analgesic properties, particularly at sub-anesthetic doses. Its integration into opioid-free anesthesia (OFA) protocols has demonstrated significant benefits. Pérez et al. (2021) studied ketamine infusion following bariatric surgery and reported significantly lower postoperative opioid consumption in the ketamine group compared to the control group [5].

Given the importance of opioid-sparing approaches to reduce complications such as respiratory depression and PONV in bariatric surgeries [6, 7], this study aimed to evaluate the effects of intraoperative ketamine versus opioids on postoperative pain and recovery in patients undergoing laparoscopic sleeve gastrectomy.

Methods

Study Design and Setting

This double-blind, randomized clinical trial was conducted at Baqiyatallah Hospital from April 2022 to April 2023.

Participants

Inclusion Criteria

Morbidly obese patients (BMI ≥40 kg/m² or ≥35 kg/m² with obesity-related comorbidities) scheduled for laparoscopic sleeve gastrectomy, aged 18–65 years, without diabetes, hypertension, hypothyroidism, neuropsychiatric disorders (including seizure history), or chronic medication use (e.g., hypoglycemics, antihypertensives, antidepressants).

Exclusion Criteria

Intraoperative complications necessitating protocol deviation. Patient/surgeon/anesthesiologist withdrawal. Drug addiction history or unavailability of study medications.

Randomization and Blinding

Patients were randomly assigned (1:1) to the ketamine or opioid group using a computer-generated random number table. An independent statistician prepared sequentially numbered, sealed opaque envelopes containing group assignments. The supervising professor provided identical 5 mL syringes labeled

"Bolus" and "Infusion," ensuring the blinding of patients, anesthesiologists, and outcome assessors.

Interventions

Preoperative Protocol:

The night before surgery, patients received standardized education on postoperative pain assessment (Visual Analog Scale, VAS) and provided written informed consent.

Anesthesia Protocol

Induction: Premedication with 2 mg midazolam and two µg/kg fentanyl. Propofol (2 mg/kg, ideal body weight) and atracurium (0.5 mg/kg, total body weight) were administered. Ventilation (airway pressure: 30 cm H_2O) preceded intubation with cuffed tubes (size 7.5/8).

Maintenance: Propofol infusion (150–200 µg/kg/min) and oxygen (4 L/min) were used. Trinitroglycerin was used as needed to manage hemodynamic targets (systolic BP within 25% of baseline).

Group-Specific Interventions

Ketamine Group: Bolus of 0.5 mg/kg ketamine over 5 minutes, followed by 0.5 mg/kg/hour infusion.

Opioid Group: Bolus of 10 mg morphine sulfate over 5 minutes, followed by remifentanil infusion (0.25 µg/kg/min). Both Groups: Received 8 mg dexamethasone, 30 mg ketorolac, and 80 mg pentoprazol (intraoperative), and 4 mg ondansetron (intraoperative). Neuromuscular blockade reversal with neostigmine/atropine.

Postoperative Management

Recovery room: Continuous SpO_2, BP, and HR monitoring; oxygen via face mask (6–8 L/min).

The pain was managed with 2 mg morphine titrated every 15 minutes for VAS >4.

Outcome Measures

Primary Outcomes

Postoperative pain (VAS) and total morphine consumption in recovery. Recovery time (extubation to Aldrete score ≥9).

Secondary Outcomes

Intraoperative drug doses (propofol, trinitroglycerin).

Incidence of nausea, vomiting, hallucinations, or delirium (assessed via binary yes/no).

Data Collection

A standardized checklist recorded demographics (age, weight, height, sex), intraoperative variables (drug doses, surgery duration), and postoperative outcomes (pain scores, complications).

Sample Size Calculation

Based on comparing postoperative nausea proportions (anticipated 3% ketamine vs. 30% opioid groups; α=0.05, β=0.2), 26 patients/group were required. Accounting for 20% attrition, 33 patients/group were enrolled.

Ethical Considerations

Informed consent emphasized voluntary participation and withdrawal rights. Confidentiality was maintained through anonymized data collection. The study protocol was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (Code: IR.BMSU.BAQ.REC.1403.040). The trial was prospectively registered (IRCT [IRCT20240424061560N1]).

Statistical Analysis

Data were analyzed using SPSS v24. Normality was assessed via Shapiro-Wilk. Continuous variables (mean ± SD) were compared with independent t-tests (normal distribution) or Mann-Whitney U-tests (non-parametric). Categorical variables (frequency, %) were analyzed using chi-square or Fisher's exact tests. Significance was set at $p<0.05$.

Results

The study included 66 patients, 18 males (26.7%) and 48 females (73.3%). Gender distribution was balanced between the opioid and ketamine groups. The overall mean age was 37.76 ± 9.8 years (range: 21–61 years), with no significant difference between the opioid group (38.40 ± 10.83) and ketamine group (37.13 ± 8.95; $p > 0.5$). BMI values were similar between groups ($p = 0.891$). Table 1 presents gender distribution, age, BMI, duration of surgery, propofol and TNG doses, and wake-up time.

The opioid group had a longer mean operative time (110 minutes vs. 101.90 minutes), though this difference was not statistically significant ($p = 0.185$). The opioid group required significantly less intraoperative propofol (603.9 mg vs. 808.3 mg; $p = 0.03$). Trinitroglycerin (TNG) Use: No patients in the opioid group required TNG, whereas all patients in the ketamine group received TNG (mean dose: 2.03 mg). Time to extubation was marginally shorter in the

opioid group (16.03 minutes vs. 16.1 minutes), but this difference was not significant (p = 0.914) (Table 1).

The average heart rate during the surgery in the Ketamine group was 89.36 beats per minute, while in the opioid group, it was 72.83 beats per minute (P=0.024). The average systolic blood pressure during the surgery was significantly higher in the Ketamine group (132.33 mmHg) compared to the opioid group (120.90 mmHg) (P=0.0190). However, there was no significant difference in the mean diastolic blood pressure between the two groups during the surgery. The diastolic blood pressure was 83.43 mmHg in the Ketamine group and 82.90 mmHg in the opioid group (P =0.391).

There were no statistically significant differences between the Opioid and Ketamine groups at any time (P>0.05). Both groups showed similar distributions of VAS scores at all measured times (Table 3).

Table 1: Comparison of demographic and clinical characteristics between the Opioid and Ketamine groups.

Variable		Opioid	Ketamine	P Value
Gender	Male	9 (27.3%)	9 (27.3%)	---
	Female	24 (72.7%)	24 (72.7%)	
Age		38.40 ± 10.83	37.13 ± 8.95	0.623
BMI		41.97 ± 4.99	42.15 ± 4.99	0.891
Duration of Surgery (minutes)		110 ± 25.02	101.90 ± 21.10	0.185
Propofol Dose (mg)		603.94 ± 177.98	808.33 ± 227.08	0.03
TNG Dose (mg)		-	2.03 ± 1.05	-
Wake-up Time (minutes)		16.03 ± 4.89	16.17 ± 4.49	0.914

Table 2: Comparison of hemodynamic parameters before anesthesia induction and during the procedure between the Opioid and Ketamine groups.

Hemodynamic Parameter	Opioid	Ketamine	P Value
Before Anesthesia Induction			
Heart Rate	72.83 ± 6.06	74.30 ± 4.71	0.30
Systolic Blood Pressure	120.90 ± 10.28	120.50 ± 12.86	0.895
Diastolic Blood Pressure	76.36 ± 5.39	75.13 ± 6.12	0.411
Respiratory Rate	13.90 ± 1.02	13.50 ± 1.07	0.189
During the Procedure			
Heart Rate	72.83 ± 6.06	89.36 ± 4.71	0.024
Systolic Blood Pressure	120.90 ± 10.28	132.33 ± 12.86	0.019
Diastolic Blood Pressure	82.90 ± 4.82	83.43 ± 3.06	0.391

Table 3: Comparison of VAS scores between the Opioid and Ketamine groups at different time points during the recovery period.

VAS Score	Opioid	Ketamine	P Value
At Entry (Before Treatment)			
1-3	8 (24.24%)	7 (21.21%)	0.431
4-6	21 (63.64%)	23 (69.70%)	
7-10	4 (12.12%)	3 (9.09%)	
At 15 Minutes 1st			
1-3	7 (21.21%)	8 (24.24%)	0.330
4-6	22 (66.67%)	23 (69.70%)	
7-10	4 (12.12%)	2 (6.06%)	
At 15 Minutes 2nd			
1-3	6 (18.18%)	11 (33.33%)	0.578
4-6	22 (66.67%)	20 (60.61%)	
7-10	5 (15.15%)	2 (6.06%)	
At 15 Minutes 3rd			
1-3	4 (12.12%)	14 (42.42%)	0.279
4-6	23 (69.70%)	18 (54.55%)	
7-10	6 (18.18%)	1 (3.03%)	
At 15 Minutes 4th			
1-3	4 (12.12%)	16 (48.48%)	0.370
4-6	21 (63.64%)	16 (48.48%)	
7-10	8 (24.24%)	1 (3.03%)	

No statistically significant differences existed between the Opioid and Ketamine groups for any of the variables assessed. VAS scores at both entries to recovery (P = 0.542) and during the entire recovery period (P = 0.320), morphine dose in recovery (P = 0.884), and recovery time (P = 0.297) showed similar results between the two groups (Table 4).

Table 4: Comparison of recovery parameters between the Opioid and Ketamine groups.

Variable	Opioid	Ketamine	P Value
VAS Score (At Entry to Recovery)	4.72 ± 0.89	4.21 ± 0.34	0.542
VAS Score (During Entire Recovery)	3.98 ± 0.92	3.72 ± 0.71	0.320
Morphine Dose in Recovery (mg)	2.40 ± 1.69	2.33 ± 1.82	0.884
Recovery Time (minutes)	58.66 ± 9.46	55.50 ± 13.47	0.297

Nausea in Recovery

There was no significant difference in the incidence of nausea between the two groups (p = 0.389). In the Opioid group, 33.3% (11 out of 33) of participants experienced nausea, while 26.7% (9 out of 33) of participants in the Ketamine group reported nausea. The majority in both groups did not experience nausea, with 66.7% (22 out of 33) in the Opioid group and 73.3% (24 out of 33) in the Ketamine group remaining free of nausea.

Vomiting in Recovery

No participants in either the Opioid or Ketamine groups reported vomiting during recovery. All participants in both groups (100%) did not experience vomiting, making this symptom absent.

Hallucinations in Recovery

A significant difference was observed in the occurrence of hallucinations, with the Ketamine group showing a notably higher incidence (p < 0.001). None of the participants in the Opioid group reported hallucinations, while 33.3% (11 out of 33) of participants in the Ketamine group experienced hallucinations.

Consequently, 100% of the Opioid group did not experience hallucinations, while 66.7% (21 out of 33) of the Ketamine group did not report any hallucinations (Table 5).

Table 5: Comparison of adverse effects during recovery between Opioid and Ketamine groups

Parameter	Opioid	Ketamine	P value
Nausea in Recovery			
Yes	11 (33.3%)	9 (26.7%)	0.389
No	22 (66.7%)	24 (73.3%)	
Vomiting in Recovery			
Yes	0 (0%)	0 (0%)	---
No	33 (100%)	33 (100%)	
Hallucinations in Recovery			
Yes	0 (0%)	11 (33.3%)	<0.001
No	33 (100%)	21 (66.7%)	

Discussion

In this study, there were no significant demographic differences between the two groups. Both groups had an equal distribution of males and females, and the age and BMI differences were not statistically significant. Hemodynamic parameters before anesthesia induction, including Spo2, blood pressure, respiratory rate, and heart rate, showed no significant differences. However, during surgery, the ketamine group had a significantly higher heart rate and systolic blood pressure compared to the opioid group. The dose of propofol was lower in the opioid group, and all ketamine group patients received TNG, whereas no opioid group patients did.

Surgical duration and recovery time were longer in the opioid group, but these differences were not statistically significant. Pain scores upon entering recovery and throughout the recovery period showed no significant differences between the groups. The occurrence of mild, moderate, or severe pain at various time points in recovery did not differ significantly between the groups. Morphine consumption during recovery was similar between the groups, with no significant difference. Nausea occurred more frequently in the opioid group, while hallucinations were more common in the ketamine group. No patients in either group had Spo2 below 92%, and recovery duration was not significantly different.

The findings of this study align with previous research on the use of ketamine as an effective non-opioid analgesic during and after laparoscopic sleeve gastrectomy (LSG) surgery. Several studies have demonstrated that ketamine infusion during surgery significantly reduces postoperative pain and opioid consumption, particularly in the early postoperative period. For instance, Mehta et al. found that ketamine infusion during gastric bypass surgery provided better pain control compared to bolus fentanyl administration during surgery combined with hydromorphone at the end of the procedure. Their study highlighted that ketamine significantly reduced morphine consumption in the first 24 hours postoperatively, with the most pronounced benefits observed within the first 6 hours after surgery. No adverse effects related to ketamine were reported in their study [9]. Similarly, Seman et al. [10] reported that patients receiving ketamine during laparoscopic gastric bypass surgery experienced lower pain scores in the first 24 hours, greater satisfaction with pain management, and improved ability to perform daily activities after discharge. The use of low-dose ketamine bolus (0.3 mg/kg) combined with intraoperative infusion (0.2 mg/kg/hr) was associated with reduced postoperative opioid consumption.

The study by Sollazzi et al. [11] further supports these findings, demonstrating that a combination of ketamine (0.5 mg/kg) and clonidine (3 µg/kg) administered preoperatively significantly reduced pain scores at 6

hours postoperatively and decreased tramadol consumption during recovery compared to intraoperative fentanyl. However, no significant difference in opioid requirements was observed at 12 hours postoperatively. Similarly, Ibrahim et al. [12] reported that while patients receiving fentanyl had significantly lower pain scores in the first 6 hours postoperatively, no significant difference was observed at 24 hours. These findings suggest that ketamine's analgesic benefits are most prominent in the early postoperative period.

In contrast, some studies have reported no significant difference in opioid consumption between ketamine and placebo groups. For example, Sanjib et al. [13] found no significant difference in opioid consumption within 24 hours postoperatively among patients receiving ketamine bolus (0.5 mg/kg), a combination of ketamine and magnesium, or placebo. Similarly, Yasemin et al. [14] reported that patients receiving lidocaine infusion had lower pain scores and shorter hospital stays compared to those receiving ketamine or dexmedetomidine. Interestingly, the ketamine group required significantly more opioids on the first postoperative day. However, Ting et al. [15] recently demonstrated that ketamine infusion (0.2 mg/kg/hr) during LSG significantly reduced pain intensity at 1, 2, 6, and 12 hours postoperatively, decreasing the need for analgesics.

A meta-analysis by Chaouch et al. [16] involving seven randomized controlled trials with 412 bariatric surgery patients found that ketamine significantly reduced total opioid consumption in the first 24 hours postoperatively and provided lower pain scores at 4 and 8 hours compared to placebo. However, no significant differences were observed at 12 and 24 hours. These findings are consistent with the growing body of evidence supporting the use of OFA in bariatric surgery as part of Enhanced Recovery After Surgery protocols. OFA has been associated with reduced hospital stays, lower postoperative opioid consumption, fewer readmissions, and decreased PONV [17-19].

PONV remains one of the most common postoperative complications, particularly in laparoscopic procedures. Risk factors include female gender, age under 50, and history of motion sickness, obesity, anxiety, and type of surgery, general anesthesia, and opioid use. Laparoscopic cholecystectomy, gynecological surgeries, and prolonged surgical duration are associated with higher PONV risk [20]. Regional anesthesia has been shown to reduce PONV risk by ninefold compared to general anesthesia [21]. In our study, the incidence of nausea was 13.3% in the ketamine group and 16.7% in the opioid group, with no cases of vomiting reported. This is consistent with the findings of Brinck et al. [22], who reported a 0.88% incidence of nausea following ketamine use. Ding et al. [23] demonstrated that combining ketamine with reduced-dose morphine (one-fourth to two-thirds of the standard dose) improved pain control, reduced PONV, and enhanced recovery. Similarly, Ziemann et al. (24) found that opioid-free anesthesia in bariatric surgery reduced PONV more effectively than triple antiemetic prophylaxis.

Regarding adverse effects, Akbari et al. [8] reported a higher incidence of sleep disturbances and hallucinations in patients receiving ketamine alongside opioids, although the difference was not statistically significant. In our study, hallucinations occurred in 16.7% of patients, with a significantly higher incidence in the ketamine group compared to the opioid group. However, López et al. [6] found no significant difference in postoperative confusion or changes in consciousness between patients receiving ketamine and opioids after mastectomy surgery.

Prolonged surgical duration is a known risk factor for increased postoperative complications. Studies have shown that every additional minute of surgery increases the risk of complications by 1%, with a 21% increase in risk for every additional hour [25]. In our study, the surgical duration was shorter in the ketamine group, although the difference was not statistically significant. Patients receiving ketamine also had a shorter recovery room stay, but this difference was not significant either. These findings are consistent with the meta-analysis by Chaouch et al. [16], which reported shorter hospital stays in the ketamine group compared to placebo despite a higher incidence of PONV and hallucinations.

Ketamine appears to be a valuable adjunct in reducing postoperative pain and opioid consumption, particularly in the early postoperative period. However, its benefits must be weighed against potential side effects such as hallucinations and PONV. Further large-scale studies are needed to optimize ketamine dosing and administration protocols to maximize its analgesic benefits while minimizing adverse effects.

Conclusion

In laparoscopic sleeve gastrectomy surgery, the use of ketamine compared to opioids did not show a significant difference in pain scores, opioid consumption, or the incidence of postoperative nausea and vomiting during recovery. However, the propofol consumption was significantly lower in the opioid group compared to the ketamine group. Additionally, systolic blood pressure and heart rate were significantly higher in the ketamine group than in the opioid group. Notably, the incidence of hallucinations was significantly greater in the ketamine group compared to the opioid group. These findings suggest that while ketamine may offer certain hemodynamic advantages, its use is associated with a higher risk of adverse effects such as hallucinations, which should be carefully considered in clinical practice.

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Conflict of Interest Disclosures
There is no conflict of interest.

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None.

Authors' Contributions
The authors equally worked in this study.

Ethical Statement
Informed consent emphasized voluntary participation and withdrawal rights. Confidentiality was maintained through anonymized data collection. The study protocol was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (Code: IR.BMSU.BAQ.REC.1403.040). The trial was prospectively registered (IRCT [IRCT20240424061560N1]).

Declaration of Generative AI and AI-assisted technologies
None.

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