

## Prospective Study



# Analgesic Low-Dose Ketamine Infusions and Central Nervous System Adverse Effects: A Prospective Cohort Study

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**Background:** Low dose ketamine infusions (LDKI) may provide adequate adjuvant analgesia while reducing postoperative opioid consumption in specific populations, such as patients with opioid tolerance or high intensity postoperative pain. However, there is currently limited data on the incidence of central nervous system adverse effects such as delirium, hallucinations, agitation, sedation, or nightmares using LDKI in treating postoperative pain.

**Objectives:** We aimed to compare the incidence of central nervous system adverse effects in patients receiving an LDKI compared with patients not receiving an LDKI for the first postoperative 48 hours.

**Study Design:** Unicentric prospective cohort comparative study.

**Setting:** An academic university hospital.

**Methods:** Patients older than 18 who underwent major orthopedic, abdominal, or thoracic surgery were grouped into those who received an LDKI (LDKI group, n = 101), and patients who did not receive ketamine (non-K group, n = 138) based on the responsible anesthesiologist decision. The LDKI group received a 0.1 mg/kg/h ketamine infusion as part of a multimodal analgesic plan.

The primary outcome was a composite of postoperative LDKI-related central nervous system adverse effects (delirium, hallucinations, or nightmares) within the first 48 hours after exposure compared with the non-K group. The secondary outcomes were pain intensity and cardiovascular variables (blood pressure and heart rate).

**Results:** There were no differences in cognitive dysfunction (delirium), agitation or sedation between groups ( $P > 0.05$ ). The primary composite objective of central nervous system symptoms occurred in 12.9% of the LDKI group compared with 2.2% in the non-K group. The adjusted risk of psychomimetic symptoms using propensity score matching was an odds ratio of 4.84 (95% CI, 1.33 – 17.76) with a  $P$  value  $< 0.016$ . The cumulative incidence of nightmares (8.9% vs 0.72%,  $P = 0.001$ ) and hallucinations (6.8% vs 2.2%,  $P = 0.071$ ) were both higher in the LDKI group.

Hemodynamic variables were not statistically different between groups. Pain level was significantly lower in the LDKI group ( $P = 0.03$ ), however, both groups presented a mean Visual Analog Scale score below 4 mm.

**Limitations:** Our study is limited by its observational method, since no intervention was assigned by the investigator.

**Conclusions:** An LDKI (0.1 mg/kg/h) for postoperative pain is associated with a low incidence of minor central nervous system effects, i.e., nightmares and hallucinations. There is no significant association with major central nervous system adverse effects, such as delirium, sedation, or agitation, supporting its safety as an adjuvant in multimodal analgesia.

**Key words:** Ketamine, adverse effects, delirium, postoperative pain, multimodal analgesia, central nervous system, opioid-sparing drug

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Low-dose ketamine infusion (LDKI) is an opioid-sparing analgesic option that has shown effectiveness as part of a multimodal approach for treating postoperative pain (POP) (1,2). Ketamine is a phencyclidine derivative that predominately affects N-methyl-D-aspartate receptors via noncompetitive antagonism. This drug prevents central sensitization and long-term potentiation in surgical pain models (3, 4). LDKI has gained renewed interest for POP treatment in the last decade due to its ability to reduce opioid consumption up to 40%, pain intensity, and nausea and vomiting compared with a control group (5,6).

Research has shown that prolonging administration of LDKI 24 to 48 hours for POP analgesia may reduce hyperalgesia after mechanical/surgical stimuli (7-9). This effect of a perioperative LDKI may be the reason for better pain control in opioid-dependent patients with chronic pain undergoing surgery (10-12). An additional effect of adjuvant ketamine for analgesia is decreased activation of the anterior cingulate cortex modulating the affective response to pain (13).

A potential long-term benefit of an LDKI in some surgical procedures is its ability to reduce the risk of chronic postsurgical pain (14,15). However, data to demonstrate the preventive role of an LDKI in chronic postsurgical pain has been controversial.

Despite ketamine's clear benefits in the aforementioned clinical scenarios, a dose-dependent relationship with the central nervous system (CNS) and cardiovascular adverse effects has been reported (16,17). Available clinical studies describe CNS adverse effects occurring more frequently, mostly after administering anesthetic doses of ketamine (18).

In the perioperative setting, LDKIs have been described as being 0.3 mg/kg/h or lower (6,19). The most commonly reported CNS adverse effects for ketamine are hallucinations, nightmares, delirium, sedation, agitation, and rarely, dissociative states. These positive symptoms are clearly dose-dependant (20,21). Limited data exist concerning the potential CNS adverse effects associated with an LDKI (1). Currently, contraindications for ketamine use include poorly controlled psychotic conditions, schizophrenia, and active substance abuse. Liver dysfunction has been associated with repeated exposure and high doses of ketamine, and should be avoided in this scenario (1,12,22). However, questions remain regarding the optimal parameters for patient selection and drug-dosing regimens of an LDKI with regard to major neuropsychiatric adverse effects that may compromise recovery of patients with POP.

Previous data of CNS adverse effects associated with an LDKI in the postoperative setting are often derived from spontaneous patient reports, not graded for severity or interrogated by validated instruments. Most trials are relatively small and intended to measure analgesia or opioid consumption as the main outcome using an LDKI. The Confusion Assessment Method scale and Richmond Agitation-Sedation Scale are validated questionnaires to detect neuropsychiatric side effects in clinical practice and research (23-25). In our study, we aimed to describe CNS adverse effects with validated scales post LDKI administration when administered up to 48 hours of postoperative analgesia.

## METHODS

### Study Design

This is a prospective cohort comparative study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Our study was approved by the Institutional Review Board of the Hospital San Vicente Fundación and written informed consent was obtained from all patients who participated in the study. The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03979105).

We aimed to compare the incidence of central nervous system adverse effects in patients receiving an LDKI compared with patients not receiving an LDKI for the first postoperative 48 hours. Components of the composite primary objective were cognitive dysfunction (delirium), nightmares, and hallucinations. Other CNS adverse effects evaluated in our study were agitation and sedation. Secondary objectives were pain intensity and cardiovascular variables (blood pressure and heart rate) measured in both groups. The LDKI intervention was part of a multimodal analgesia with opioids, as per the protocol under the supervision of our acute pain service.

### Study Population

Patient inclusion criteria were 18 years or older, surgical POP, American Society of Anesthesiologists physical status  $\leq 3$  after undergoing major orthopedic, abdominal, or thoracic surgery from August 2021 through December 2022. Patients were grouped into those who received an intravenous LDKI ( $n = 101$ , LDKI group), and patients who did not receive ketamine ( $n = 138$ , non-K group) based on the responsible anesthesiologist's decision. Our institutional protocol calls for LDKIs for 24–48 hours to treat POP as part of

a multimodal regimen of analgesia, which is indicated in surgeries that are associated with intense pain or in chronic pain treated with opioids. Exclusion criteria were psychiatric disorders, lack of verbal communication, cognitive impairment, uncontrolled hypertension, recent myocardial infarction, dysrhythmia, angina, or increased intraocular or intracranial pressure.

### Study Procedures

A multidisciplinary acute pain service was contacted in order to find patients meeting our inclusion criteria. Patients' demographic characteristics were collected preoperatively. In the postanesthesia care unit, patients in the LDKI group received continuous ketamine infusions at a dose of 0.1 mg/kg/h, up to a maximum of 48 hours postsurgery. Ketamine infusion was initiated by a registered nurse, and an anesthesiologist was available throughout the treatment. The non-K group did not receive ketamine as part of their multimodal regimen.

A bedside questionnaire was completed that included delirium (cognitive dysfunction) measured with the Confusion Assessment Method scale (23,24). This scale assesses 4 features: 1) acute onset or fluctuating course; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness. It was validated to the Spanish version Confusion Assessment Method-S (25) (Appendix 1). The diagnosis of delirium by the Confusion Assessment Method scale requires a positive response to features one and 2 plus either 3 or 4; in these cases, the patients were considered as presenting a postoperative cognitive dysfunction. Nightmares were defined as the presence of unpleasant/bad dreams; hallucinations were defined as seeing, hearing or feeling things that aren't actually present. Each of the components of the composite outcome was also analyzed separately.

Sedation or agitation were measured with the Richmond Agitation-Sedation Scale Spanish version (25,26). Secondary objectives were pain level measured with the Numeric Rating Scale (NRS) (0 = no pain and 10 = worst pain) and hemodynamic variables: systolic blood pressure, diastolic blood pressure, and heart rate measured with an automatic digital monitor (Mindray MEC 1200, Bio-Medical Electronics Co, Ltd) every 6 hours by the nurse in charge of inpatient care. Variables were measured at postoperative 24 and 48 hours. When an LDKI side effect was reported as bothersome or compromising the patient's safety, the medical team suspended the ketamine infusion.

### Sample Size Calculation

Nonprobability sampling of consecutive cases was planned during the study period. Based on the data and studies provided by the systematic review by Brinck et al (27), when analyzing studies where these types of adverse effects were evaluated, it was found that for a composite outcome of psychomimetic symptoms, the absolute difference between both groups was up to 10%. For the non-K group, the incidence was 5.1% compared to 14.8% for the LDKI group. For a power of 87% and a Type I error of 0.05, a sample of 239 patients was required to statistically demonstrate differences in the events studied. The STATA 14.0 program (StataCorp LLC) was used for the sample design.

### Statistical Analysis

Clinical and demographic characteristics are presented using measures of central tendency and dispersion. Categorical variables are presented in absolute and relative frequencies, while quantitative variables are described with their mean and SD if they followed a normal distribution assumption based on the Shapiro-Wilk test; otherwise, medians and interquartile ranges are reported. Table 1 shows the statistical summaries of the variables by group with their respective *P* values.

To determine the incidence of psychomimetic symptoms, the absolute and relative frequencies of the event were calculated in each group. For POP, the NRS was quantified in each group as means and SDs. For cardiovascular variables, systolic blood pressure, diastolic blood pressure, and heart rate were quantified in each group as means and SDs.

To estimate the association between ketamine infusion and the incidence of psychomimetic symptoms, an unadjusted analysis was performed using the odds ratio as a point estimator, along with their respective 95% CIs, and  $\chi^2$  hypothesis test. Subsequently, to control for potential confounding variables, age, American Society of Anesthesiologists classification, and systemic opioid use were taken into account. Matching between the LDKI group and the non-K group was performed using the propensity score matching method for the aforementioned covariates. Adequate adjustment between groups was considered when the standardized absolute mean difference was less than 0.1. An adjusted estimation by confounding variables was then performed using binary logistic regression, with the calculated probability of belonging to the LDKI group through propensity score matching as the adjustment variable for one of these variables: age, American

Table 1. Clinical characteristics of patients undergoing ketamine infusion.

Variable	Ketamine Group (n = 101)	Non-ketamine Group (n = 138)	P Value <sup>a</sup>
Age (years), u (SD)	45.86 (15.61)	47.49 (15.85)	0.431
Gender, n (%)			
- Women	45 (44.6%)	62 (44.9%)	0.954
- Men	56 (55.4%)	76 (55.1%)	
Weight (kg), u (SD)	65.08 (12.14)	69.45 (12.42)	0.010
ASA status, n (%)			
- I	38 (37.6%)	29 (21%)	0.005
- II	45 (44.6%)	68 (49.3%)	0.472
- III	17 (16.8%)	41 (29.7%)	0.022
Presurgical diagnosis, n (%)			
- Fracture and/or trauma to bone and/or joints	34 (33.7%)	89 (64.5%)	< 0.001
- Acute abdomen pain	10 (9.9%)	18 (13.0%)	0.456
- Thoracic/abdominal trauma	7 (6.9%)	2 (1.4%)	0.028
- Peripheral artery disease	9 (8.9%)	6 (4.3%)	0.151
- Major oncological disease	20 (19.8%)	16 (11.6%)	0.080
- Radiculopathy/spine pathology	15 (14.8%)	3 (2.2%)	< 0.001
- Genitourinary pathology	6 (5.9%)	4 (2.9%)	0.246
Procedure and/or surgical access route, n (%)			
- Lower limb <sup>b</sup>	40 (39.6%)	82 (59.4%)	0.003
- Upper limb <sup>b</sup>	5 (4.9%)	7 (5.1%)	0.966
- Laparotomy	32 (3.2%)	34 (24.6%)	0.229
- Thoracotomy/sternotomy	6 (5.9%)	4 (2.9%)	0.246
- Posterior column	15 (14.8%)	3 (2.2%)	< 0.001
- Amputation	3 (2.9%)	8 (5.8%)	0.303
Comorbidities, (%)			
- High blood pressure.	24 (23.8%)	31 (22.5%)	0.485
- Diabetes	11 (10.9%)	17 (12.3%)	0.480
- Chronic obstructive pulmonary disease	0 (0)	2 (1.4%)	0.243
- Kidney disease	1 (1%)	2 (1.4%)	0.533
- Cerebrovascular disease	0 (0%)	2 (1.4%)	0.243
- Obesity	8 (7.9%)	14 (10.1%)	0.220
- Dyslipidemia	2 (2%)	9 (6.5%)	0.107
Smoking, n (%)			
- Active	3 (3%)	12 (8.7%)	0.103
- History of smoking	0 (0%)	12 (8.7%)	0.010
Regional techniques, n (%)			
- Epidural	12 (11.9%)	20 (14.5%)	0.558
- Peripheral blocks	5 (4.9%)	50 (36.2%)	< 0.001
Baseline Visual Analog Scale Score, u (SD)	3.5 (2.79)	3.3 (2.63)	0.475
Postoperative adjuvant analgesics, n (%)			
- Acetaminophen	50 (49.5%)	63 (45.7%)	0.404

Society of Anesthesiologists classification, and intravenous opioid use. The respective odds ratios with their 95% CIs were calculated. A *P* value < 0.05 was considered statistically significant for all estimators. IBM SPSS Statistics 29.0 (IBM Corporation) was used for statistical calculations.

### Risk of Bias

To avoid selection bias, the same inclusion criteria were employed for both groups. Additionally, to control for potential confounding bias, a prospective matching process based on variables such as gender, age groups, and surgical model was conducted. Furthermore, following patient recruitment, the propensity score technique was employed to control for these confounding variables within a binary logistic regression model.

To mitigate measurement bias, the clinical outcome measurements and variables of interest were conducted by an anesthesiology resident from the University of Antioquia. Identical data collection formats and information, as well as the same patient follow-up structure, were used for individuals undergoing these types of analgesic techniques.

### RESULTS

A total of 239 patients were evaluated in the study; 101 in the LDKI group and 138 in the non-

K group. Table 1 presents the demographic and clinical variables of the population. The majority of patients were men, with a mean age of 45 years in the LDKI group and 47 in the non-K group. The main comorbidity was hypertension followed by diabetes.

In both groups, the main reason for surgical intervention was orthopedic procedures in the lower extremity, accounting for 39.6% in the LDKI group

and 59.4% in the non-K group. Opioids, acetaminophen and nonsteroidal anti-inflammatory drugs were the most common multimodal regimen observed in the study. Peripheral nerve blocks predominated in the non-K group (36.2%) versus 4.9% in the LDKI group; both groups received epidural analgesia in similar proportions.

There were no statistically significant differences in cognitive dysfunction (delirium), agitation, or sedation between groups. The cumulative incidence of delirium was 1.98% and 0.72% ( $P = 0.3891$ ); sedation, 1.9% and 0.7% ( $P = 0.38$ ); and agitation, 1.9% and 1.5% ( $P = 0.56$ ) for the LDKI and non-K groups respectively. The primary composite of CNS symptoms—delirium, hallucinations or nightmares—occurred in 12.9% (13/101) in the LDKI group compared with 2.2% (3/138) in the non-K group (Fig. 1), with an unadjusted odds ratio of 6.64 (95% CI, 1.97–22.33;  $P = 0.0016$ ). Nightmares occurred in 8.9% vs 0.72% ( $P = 0.001$ ) and hallucinations 6.8% vs 2.2% ( $P = 0.0716$ ) in the LDKI and non-K groups respectively.

Table 2 presents the adjustment of potential confounding variables using propensity score matching. All variables had a Cohen's d value less than 0.1. The adjusted risk of psychomimetic symptoms using propensity score matching was an odds ratio of 4.84 (95% CI, 1.33–17.76) with a  $P$  value  $< 0.016$ .

Hemodynamic variables were not statistically different for systolic blood pressure, mean arterial pressure, diastolic blood pressure, or heart rate (Fig. 2). Pain level was significantly lower in the LDKI group ( $P = 0.03$ ), however, both groups presented a mean Visual Analog Scale score below 4 (Table 3).

## DISCUSSION

In this prospective, comparative study of 239 pa-

Table 1 cont. *Clinical characteristics of patients undergoing ketamine infusion.*

Variable	Ketamine Group (n = 101)	Non-ketamine Group (n = 138)	P Value <sup>a</sup>
- Dipyron (not USFDA approved)	4 (4%)	93 (67.4%)	$< 0.001$
- Nonsteroidal anti-inflammatory drugs.	33 (32.7%)	57 (41.3%)	0.215
- Tramadol	40 (39.6%)	21 (15.2%)	$< 0.001$
- Intravenous strong opioid <sup>c</sup>	40 (39.6%)	53 (38.3%)	0.403
- Intrathecal strong opioid <sup>c</sup>	6 (5.9%)	68 (49.3%)	$< 0.001$
- Magnesium sulfate	1 (1%)	7 (5.1%)	0.017
- Lidocaine	0 (0%)	8 (5.6%)	0.014

Abbreviations: ASA, American Society of Anesthesiologists

a  $\chi^2$  heterogeneity test.

b Open reductions and/or osteosynthesis; arthroscopies; joint replacements.

c Strong opioid: morphine, hydromorphone, oxycodone

tients assessing LDKIs for postsurgical analgesia, few

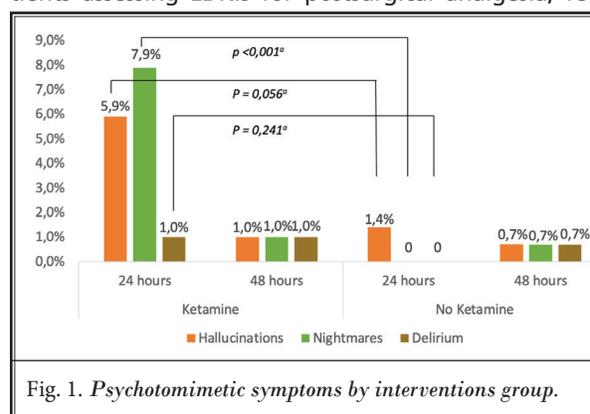


Fig. 1. *Psychomimetic symptoms by interventions group.*

CNS adverse effects were observed in both groups. The composite outcome of delirium, agitation, and hallucinations was higher in the LDKI group (odds ratio, 4.84); it was driven only by minor CNS adverse effects, namely agitation and hallucinations, however, this finding may lack clinical significance.

Even though psychomimetic symptoms are the most frequent adverse effects reported in previous trials that used ketamine in analgesia, nightmares and hallucinations (vivid dreams) are considered minor and seldom compromise recovery (14,27-29). No differences in major CNS adverse effects—such as delirium, agitation, or sedation—were observed between groups in our study.

Consistent with our results, hallucinations and nightmares are the most frequent psychomimetic adverse effects observed post LDKI administration for POP (14,29,30). Sedation or agitation occurred in less than 2% of the patients in our study, with no significant differences observed between groups.

Table 2. Confounding variables for psychomimetic symptoms pre- and postmatching by propensity score.

Variable	Prematching			Postmatching		
	Ketamine Group n = 101	Non-ketamine Group n = 138	d	Ketamine n = 100	No ketamine n = 99	Cohen's d
Age (years), u (SD)	45.86 (15.61)	47.49 (15.85)	0.0732	45.86 (15.61)	44.10 (15.41)	0.0801
ASA status, n (%)						
- I and II	83 (82.2%)	97 (70.3%)	0.3102	83 (83%)	81 (81.8%)	0.0263
- III	17 (16.8%)	41 (29.7%)	0.3090	17 (17%)	18 (18.2%)	0.0315
Intravenous opioids, n (%)	72 (71.3%)	65% (47.1%)	0.5080	72 (72%)	72 (72.7%)	0.0156

Abbreviations: ASA, American Society of Anesthesiologists.  
Cohen's d: standardized absolute mean difference. A value less than 0.1 is considered a good match.

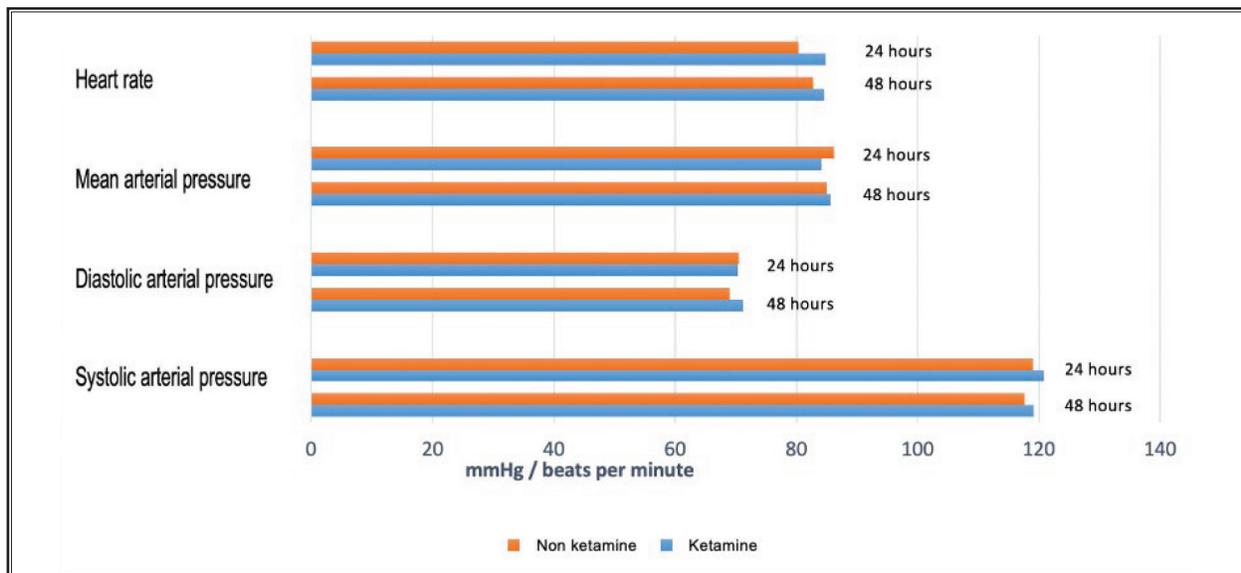


Fig. 2. Hemodynamic variables by intervention group.

Table 3. Visual Analog Scale (VAS) pain score by group.

VAS	Ketamine Group (n = 101)	Non-ketamine Group (n = 138)	Difference in means, CI 95%	P Value <sup>a</sup>
VAS Baseline, u (SD)	3.5 (2.79)	3.3 (2.63)	0.2 (0.1 to 0.5)	0.475
VAS 24 hours, u (SD)	3.14 (1.76)	3.73 (2.44)	- 0.59 (-1.12 to -0.052)	0.032
VAS 48 hours, u (SD)	1.83 (1.36)	2.89 (1.87)	-1.06 (-1.49 to -0.595)	< 0.001

<sup>a</sup>  $\chi^2$  heterogeneity test.

Our results are comparable with a retrospective, matched-cohort study conducted by Porter, et al (28) of 104 patients who underwent surgery. These patients were administered an LDKI dosage of 0.1 mg/kg/h (range 0.05–0.1 mg/kg/h); they experienced more hallucinations (5 vs zero), compared with those who were not administered ketamine. The median administra-

tion duration was 44 hours (range, 8–83 hours) (28). Similarly, in a prospective randomized controlled trial conducted by Lahtinen, et al (29), 90 patients scheduled for elective coronary artery bypass graft surgery were randomized to receive either a 75 µg/kg bolus of S(+)-ketamine followed by a continuous infusion of 1.25 µg/kg<sup>-1</sup>/min<sup>-1</sup> for 48 hours or placebo. Four out of 44 patients

(9%) in the S(+)-ketamine group developed transient hallucinations during their infusion, while none in the placebo group experienced hallucinations (29). Interestingly, patient satisfaction with the analgesic management was superior in the S(+)-ketamine-treated patients, despite having those minor CNS side effects (60% in the LDKI group vs 35% in the placebo group).

In contrast to our findings, several trials of LDKI in patients with POP did not report differences for psychomimetic adverse effects (5). In a randomized controlled trial conducted by Adrianssens, et al (31), 30 patients received patient-controlled analgesia and LDKI (0.15 mg/kg/h) or placebo up to 48 hours postsurgery. They described no differences in psychomimetic symptoms in either group (31). Similarly, Seman, et al (32) reported no differences in hallucinations or nightmares in a comparison trial of LDKI with a control group for analgesia after laparoscopic gastric bypass. The LDKI group received a 0.3 mg/kg ideal body weight ketamine bolus after induction followed by a 0.2 mg/kg/hr ketamine infusion that was continued for up to 24 hours (32).

CNS adverse effects previously reported that are associated with LDKI must be interpreted with caution; they are often derived from spontaneous patient reports or not systematically evaluated by validated instruments (1). Previous research using LDKI for POP analgesia has focused on analgesic effectiveness or opioid consumption as primary outcomes (6,12,19,28,32).

Data reporting CNS side effects from an LDKI has possibly been underpowered to detect minor adverse effects, such as nightmares or hallucinations. To the best of our knowledge, our study is the largest prospective cohort study using validated scales to measure CNS adverse effects associated with LDKI; consequently, it more accurately estimates LDKI's effect on POP analgesia.

We believe delirium/confusion is probably the most worrisome adverse effect deserving attention when evaluating CNS adverse effects related to LDKIs. Delirium has been associated with increased mortality in the postoperative period (33). Our result shows a very low incidence of delirium (less than 2%) in both the LDKI and non-K group. We evaluated delirium with the Confusion Assessment Method tool, a validated instrument that has shown equal sensitivity and higher specificity to detect delirium when compared with other instruments (34). The Confusion Assessment Method scale has been used previously to detect delirium in several studies, including ketamine during the postoperative period (35).

Our results, in agreement with previous controlled studies, suggest that maintaining LDKI doses below 0.1

mg/kg/h could reduce the risk of delirium, while still providing an adequate opioid-sparing effect and preventing hyperalgesia (7). We used a 0.1 mg/kg/h LDKI, because this dose regimen has been widely reported to have a minimum analgesic effect when administered 24–72 hours postoperatively (5,27,32).

Even though postoperative delirium may have multiple causes—for example, electrolyte imbalance, opioid analgesia, infection, or hemodynamic alterations—a dose-dependent effect of ketamine causing delirium/confusion has been reported (7). The threshold dose for LDKI-related delirium is an important confounding factor among the causes of delirium to rule out (7,21). Our results suggest that an LDKI of 0.1mg/kg/h administered beyond perioperative time does not increase the risk of delirium in patients with POP. Interestingly, other authors have suggested low dose ketamine has a role in actually decreasing postoperative delirium in postoperative scenarios (36,37).

Regarding other secondary objectives measured in our study, there were no significant differences in postoperative cardiovascular variables between the LDKI group and the non-K group: systolic blood pressure, diastolic blood pressure, and heart rate (mean). Tachycardia and hypertension are dose-related cardiovascular adverse effects of ketamine, frequently associated with anesthetic doses (38). This result is in line with recent data supporting no clinical effect of low-dose ketamine in hemodynamic response when administered for analgesia (39).

In our study, pain intensity was significantly lower among patients in the LDKI group. However, patients in both groups received different types of opioids, and therefore, the reduction in pain cannot be entirely attributed to ketamine due to this confounding variable. Nonetheless, adequate postsurgical pain control was observed in both groups (Table 2). The analgesic effect of an LDKI is consistent with findings from previous systematic reviews and recent comparative trials (5,32,35). An analysis of the dose-dependent effects of ketamine on pain processing has shown a decrease in the activation of the secondary somatosensory cortex (S2), insula, and anterior cingulate cortex (13). The midcingulate cortex, an area associated with the affective component of pain, has been linked to the potency of ketamine in modulating pain processing (13).

### Limitations

There are some limitations to our study. The inclusion criteria were patients with good general health

status. Patients with uncontrolled psychiatric or cardiovascular disease were excluded; therefore, an important issue for future research is to detect the effect of an LDKI in patients with these risk factors. Another limitation is the observational nature of our study, since no intervention was assigned by the investigator. In the future, a clinical trial with a more specific population at risk to develop CNS adverse effects—for example, in patients with psychotic states, delirium, or a history of schizophrenia—could be designed to further investigate the safety of ketamine use in these patients.

There is a trend toward using an LDKI for 24–72 hours postoperatively. Pouladar, et al (40) demonstrated the superiority of maintaining an LDKI up to 48 hours compared with ketamine via patient-controlled analgesia to reduce adverse effects in patients who underwent surgery who are chronically receiving opioids (40). Systematic reviews have shown the beneficial role of LDKIs in surgeries associated with high intensity POP such as thoracotomy, oncology surgery, etc. (27). Furthermore, data showing the beneficial effect of LDKIs in reducing hyperalgesia or chronic postsurgical pain is derived mostly from treatment up to 24–48 hours postsurgery (7,8,14). The results of our study may have an effect on a more liberal use of LDKIs in clinical practice, as suggested by recent data administering LDKIs in general wards (41).

## CONCLUSIONS

LDKI (0.1 mg/kg/h) in patients with POP is associated with a low frequency of minor CNS effects, i.e., nightmares and hallucinations. There was no significant association of LDKIs with major adverse effects like delirium, sedation, or abnormal cardiovascular response. Altogether, our results reflect a safe profile for LDKI as an adjuvant in multimodal analgesia in patients having surgery.

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## Author Contributions

Adriana M. Cadavid: conception and design, data analysis, manuscript writing. Fabian D. Casas: statistical analysis, data analysis. Julio E. Camelo: data analysis, manuscript writing. Andres Barrios: data analysis, manuscript writing. Esteban Calle: data collection, manuscript submission. Cristian D. Ramirez: data collection, manuscript writing. Luisa F Aguirre: data collection, manuscript writing. All authors read and approved the final manuscript.

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