Effect of Analgesic Low-Dose Ketamine Infusions on the Cardiovascular Response: A Retrospective Analysis

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Background: Low-dose ketamine infusion (LDKI) has shown effectiveness for treating acute pain associated with surgical and nonsurgical (traumatic, neuropathic, and acute cancer-related) origin as an adjuvant to opioids. The increasing use of LDKI as an opioid-sparing agent in multimodal analgesia requires a better understanding of its effects on the cardiovascular response, a known dose-dependent side effect of ketamine administration. We investigated the cardiovascular response of acute pain patients treated with LDKI.

Objectives: The aim of the present study was to evaluate the effect of LDKI in hemodynamic variables (blood pressure [BP] and heart rate [HR]) during LDKI analgesia for up to 48 hours of treatment in an acute pain setting. Secondary objectives were to evaluate psychomimetic effects.

Study Design: Retrospective unicentric cohort design.

Setting: The study was conducted at an academic university hospital. Methods: We conducted a single-center retrospective cohort analysis of adult patients who underwent LDKI to treat surgical and nonsurgical acute pain. We obtained data from the Hospital San Vicente Fundación Health Documentation System database and evaluated the medical records of 318 patients with surgical and nonsurgical pain. Patients received a 0.1 mg/kg/h ketamine infusion as part of a multimodal analgesic plan. Baseline systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and HR values were compared with those measured after 24 and 48 hours of treatment. Pain level and psychomimetic effects were measured at 24 and 48 hours. Cardiovascular complications and treatment duration were also recorded. Patients with a history of psychiatric, cardiovascular, or cognitive disease were excluded from the study. This study was registered in the clinicaltrials.gov database (identifier: NCT03979105).

Results: No statistical differences in SBP, DBP, MAP, or HR were observed when baseline and post-LDKI treatment values were compared (P < 0.05). When comparing hemodynamic variables after exposure to LDKI in patients with and without hypertension, we did not observe statistically significant differences in mean HR, systolic arterial pressure, diastolic arterial pressure, or MAP values at 24 and 48 hours. The frequency of severe pain was reduced from 72% on day 0 to 4.4% on day 1 and 6.2% on day 2 post-LDKI. Observed psychomimetic effects were confusion 4.39%, hallucinations 2.51%, and nightmares 1.25%. No major cardiovascular events were observed.

Limitations: This study was limited by its retrospective design, the lack of a comparative matching cohort, and the good general condition of the majority of patients included in the study.

Conclusions: LDKI (0.1 mg/kg/h) was not associated with significant changes in baseline BP or HR. Our results suggest that as an adjuvant in multimodal analgesia for surgical and nonsurgical acute pain, LDKI has a low impact on the cardiovascular response.

Key words: Ketamine, adverse effects, tachycardia, hypertension, postoperative pain, chronic postsurgical pain

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Ketamine is an N-methyl-D-aspartate-receptor antagonist shown to have an analgesic effect in acute pain (1,2). The compound is useful for decreasing opioid consumption when administered as part of a multimodal analgesic regimen in several surgical and nonsurgical pain models, particularly in patients taking opioids for chronic pain (3,4). Some trials have described the potential role for ketamine in decreasing chronic postsurgical pain (CPSP) (5,6).

Low-dose ketamine infusions (LDKIs) have garnered renewed interest as adjunct analgesics for postoperative pain (POP) analgesia (7,8). Patients administered LDKIs had lower pain scores, needed 20% to 40% less opioids, and had lessened postoperative nausea and vomiting than the control group (9). In perioperative clinical practice, LDKIs have been described as those of 0.3 mg/kg/h or less (10). In the setting of nonsurgical pain, LDKIs are increasingly being administered for treating pain associated with trauma, burns, acute neuropathic pain, and chronic pain exacerbations (2,4,11,12).

Research (7,13) has shown that administration of a single ketamine dose is not as effective as both intraoperative and postoperative administration for prolonging analgesia time and reducing opioid consumption up to 72 hours postsurgery. Additionally, a single dose of ketamine during the perioperative period failed to prevent CPSP. In contrast, previous data suggest that LDKIs for at least 24-48 hours are potentially beneficial for treating POP and reducing CPSP (7,13).

Though clear benefits of ketamine have been demonstrated, dose-dependent cardiovascular and psychomimetic side effects have been reported in the literature (14). Hemodynamic changes associated with ketamine administration are often observed after patients have been provided anesthetic doses of 1-5 mg/kg or in trauma patients prior to hospital administration (15,16). Although LDKIs have a well-demonstrated analgesic effect in acute pain, limited data exist concerning their potential cardiovascular effects including blood pressure (BP) or heart rate (HR) changes at subanesthetic doses. Currently, the major contraindications for ketamine use include poorly controlled cardiovascular disease and hepatic dysfunction (1); however, questions remain regarding the optimal parameters for patient selection and drug-dosing regimens of LDKI with regard to cardiovascular safety. Available clinical studies (1,7,21) examining the subanesthetic use of ketamine provide little guidance on contraindications for cardiovascular disease. Most trials have enrolled generally healthy individuals or relatively small samples and are therefore unlikely to detect cardiovascular issues in sensitive individuals. This study aimed to describe changes in BP and HR during LDKI analgesia for up to 48 hours of treatment in an acute pain setting.

**METHODS**

**Study Design**

This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). This 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 trial. The trial was registered at clinicaltrials.gov (NCT03979105). Data were collected from the medical records of our institution (Systems Applications and Products).

The objective of this study was to compare hemodynamic variables: systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and HR (beats/min) before and during LDKI treatment for 24 and 48 hours. MAP was derived from systolic BP (SBP) and diastolic BP (DBP) using the following formula: MAP = 1/3 (SBP-DBP) + DBP. Baseline HR, SBP, and DBP measurements were recorded prior to administering LDKI. Secondary objectives were frequency of psychomimetic side effects: hallucination, confusion, sedation, nightmares, and agitation reported after the exposure to LDKI (Table 1). Pain intensity measured with a categorical scale (absent, mild, moderate, or severe) was documented (Table 2).

**Study Population**

The patients included were 18 years or older with acute pain of surgical or nonsurgical origin who received an LDKI as per the protocol under the supervision of our acute pain service from August 2018 to December 2021. Surgical POP patients included those of the American Society of Anesthesiologists (ASA) physical status ≤ 3 after major orthopedic, abdominal, or thoracic surgery. Inpatients with nonsurgical acute pain with a diagnosis of trauma, acute neuropathic pain, burns, acute cancer pain, or a falciform pain crisis were included. Our institutional protocol calls for LDKIs for 24-48 hours to treat severe acute pain as part of a multimodal regimen of analgesia, which is indicated in operations that are associated with intense pain or acute nonsurgical pain refractory to opioids. Exclusion criteria were psychiatric disorders, lack of verbal...
communication, cognitive impairment, uncontrolled hypertension (HTN), recent myocardial infarction, dysrhythmia, angina, or increased intraocular or intracranial pressure.

**Study Procedures**

A multidisciplinary acute pain service was used to identify patients meeting inclusion criteria. A registered nurse administered a solution containing 1 mg/mL of ketamine in 0.9% sodium chloride at a dose of 0.1 mg/kg/h and an anesthesiologist was available throughout treatment. Vital signs and cardiovascular variables (SAP, DAP, and HR) were measured using an automatic digital monitor (Mindray MEC 1200; Shenzhen Mindray Bio-Medical Electronics Co, Ltd, China) every 6 hours by the nurse in charge of inpatient care. The acute pain service registered pain levels every 24 hours and psychomimetic effects reported by the patient or staff were registered in the follow-up notes during 24 and 48 hours of treatment with LDKI. When a side effect of LDKI was reported as bothersome or compromising the patient's safety, the medical team suspended the ketamine infusion.

**Statistical Analyses**

Quantitative variables were reported as means and standard deviations if they were determined to be normally distributed, which was evaluated using the Shapiro-Wilk test. If data were not normally distributed, they were reported as medians and interquartile ranges. Qualitative variables were summarized using frequencies and percentages.

Hemodynamic variables (BP, HR, and body temperature) at baseline and after (24 and 48 hours) administration of LDKI via analysis of variance (ANOVA) for repeated samples were compared; in the case of quantitative variable data nonnormality, the Friedman test was used to assess repeated samples. Hemodynamic changes were analyzed in the following subgroups:

### Table 1. Psychomimetic side effects associated with LDKI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Patients at 24 h (%)</th>
<th>Number of Patients at 48 h (%)</th>
<th>Total, n = 318 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>6 (1.88)</td>
<td>8 (2.51)</td>
<td>14 (4.39)</td>
</tr>
<tr>
<td>Nightmares</td>
<td>3 (0.94)</td>
<td>1 (0.31)</td>
<td>4 (1.25)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5 (1.57)</td>
<td>3 (0.94)</td>
<td>8 (2.51)</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (0.62)</td>
<td>1 (0.31)</td>
<td>3 (0.94)</td>
</tr>
<tr>
<td>Agitation</td>
<td>3 (0.94)</td>
<td>0 (0.9)</td>
<td>3 (0.94)</td>
</tr>
</tbody>
</table>

Abbreviations: LDKI, low-dose ketamine infusion; h, hour; n, number.

Pain level after LDKI.

<table>
<thead>
<tr>
<th>Pain Assessment, n = 318</th>
<th>Baseline n (%)</th>
<th>Ketamine Infusion at 24 h n (%)</th>
<th>Post-Ketamine Infusion at 48 h n (%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>2 (0.6)</td>
<td>15 (4.7)</td>
<td>17 (5.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (1.9)</td>
<td>225 (70.8)</td>
<td>222 (69.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>77 (24.2)</td>
<td>61 (19.2)</td>
<td>56 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>229 (72)</td>
<td>14 (4.4)</td>
<td>20 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>4 (1.3)</td>
<td>3 (0.9)</td>
<td>3 (0.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square heterogeneity test.

Abbreviations: LDKI, low-dose ketamine infusion; h, hour; n, number.

In total, 318 patients treated between March 2018 and October 2020 were identified. A total of 289 patients (89.9%) received LDKI for at least 48 hours and had complete data. Demographic data and characteristics of the population are shown in Table 3. Most patients were men (56.9%), with a mean age of 42 years. Further, 49.1% of patients were of ASA physical status I-II. The most frequently observed comorbidity was HTN (25.2%) followed by type 2 diabetes mellitus (12.3%) (Table 3). Clinical data related to LDKI are presented in Table 4. Among the study population, 62.6% were treated for nonsurgical pain in which the majority of patients experienced acute neuropathic pain (23.6%). The remaining 37% were treated for surgical pain. Adjunct analgesia was common, with a combination of opioids and acetaminophen most frequently used (38%) followed by the axonal nerve block (10%). The
mean duration of LDKI was 5 days, although a vast number of patients were discharged before this time. Infusion was suspended before 48 hours due to central nervous system side effects or other causes shown in Table 4.

No significant difference between surgical and nonsurgical groups for hemodynamic values was observed ($P = 0.505$) (Fig. 1).

No significant difference between baseline (preketamine infusion) and post-LDKI HR, SBP, DBP, and MAP values was observed (Table 5). When comparing hemodynamic variables after exposure to LDKI in patients with and without HTN, we did not observe statistically significant differences in mean HR, SAP, DAP, or MAP values at 24 and 48 hours (Table 6). Psychomimetic effects associated with LDKI were confusion 4.39%, hallucinations 2.50%, nightmares 1.25%, agitation 0.94%, and sedation 0.94% (Table 1). The proportion of patients with severe pain was reduced from 72% on day 0 to 4.4% on day 1 and 6.2% on day 2 (Table 2).

**DISCUSSION**

This study of 318 patients treated with LDKI for analgesia for both surgical and nonsurgical pain revealed no significant differences in BP or HR after up to 48 hours of treatment vs baseline. In our protocol, we used 0.1 mg/kg/h LDKI because this dose for LDKI regime has been widely reported to have an analgesic effect when administered 24-72 hours for surgical and nonsurgical pain (13,17-20).

Our results are in agreement with those of a controlled study reported by Adriæenssens et al (21) who reported the cardiovascular changes when adding an...
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infusion of 0.15 mg/kg/h ketamine for the treatment of pain after laparotomy. HR, SAP, and ventilatory frequency values between groups LDKI or control did not differ. Opioid consumption at 48 hours was significantly lower among those given ketamine vs those who were not. The study may have been limited by its small sample size (15 patients in each arm). Our data are also similar to those of Barrevel et al (3), who evaluated 64 patients undergoing nononcologic surgery. Cardiovascular side effects of therapy were compared among groups receiving continuous ketamine infusion (0.2 mg/kg/h) initiated postoperatively and continued 24 hours vs those receiving saline infusion. No adverse hemodynamic changes were observed among those given ketamine or placebo (3,22). Continuous LDKI with no initial bolus was used to treat POP and showed analgesic efficacy.

We also investigated the impact of preexisting HTN on LDKI-induced hemodynamics, revealing that a history of HTN did not significantly increase LDKI-induced SBP or DBP. Unstable or untreated hypertensive patients were not included because the risk associated with LDKI is unknown among this population and ketamine has known sympathetic nervous system effects (23).

Given that HTN and tachycardia associated with ketamine are dose dependent (24), fully understanding what is meant by “low dose” ketamine is important when assessing cardiovascular risk. To treat POP, the term “low-dose” was initially used by Schmid et al (25) in 1999 when referring to continuous intravenous administration of 1.2 mg/kg/h ketamine. Subsequently, the systematic review of Brinck et al (9) used similar LDI doses. Gorlin et al (10) described outcomes of ≤ 0.3 mg/kg/h LDKI for treating POP. For the management of nonsurgical pain, at least 2 authors (4,12) have used ≤ 0.3 mg/kg/h LDI as an intervention. Using the minimum effective analgesic dose of LDKI is important for minimizing the risk of psychoactive and cardiovascular side effects. When treating acute and POP with LDI, our observation is that a dose regimen of 0.1 mg/kg/h or less is effective for pain management and for reducing opioid consumption and hyperalgesia. Deng et al (17) showed that Visual Analog Scale scores and remifentanil consumption levels of patients given continuous 0.1 mg/kg and 0.05 mg/kg/h LDKI for 24 hours after orthopedic surgery were significantly lower than those given saline. Similarly, Arikan et al (26) showed that morphine consumption and pain levels of women scheduled for total abdominal hysterectomy who were given 0.05 mg/kg/h LDI for 48 hours were lower than those who did not receive LDI.
significantly lower than those given saline. Regarding acute, nonsurgical indications for LDKI, patients diagnosed with complex regional pain syndrome receiving a subanesthetic dose of 0.1–0.3 mg/kg/h ketamine infusions for 4-8 hours per day experienced no hemodynamic changes (4).

In other scenarios, subanesthetic ketamine has increasingly been recognized as an effective treatment for resistant depression. In 2021, a meta-analysis of hemodynamic responses to subanesthetic doses of ketamine in patients with psychiatric disorders by Vankawala et al (27) revealed modest but significant increases in BP, with an average postadministration maximum SBP of 132.48 mmHg and maximum DBP of 82.92 mmHg using a ketamine dose of ≤ 0.5 mg/kg.

With regard to the analgesic efficacy of LDKI, our results confirm a well-known analgesic effect described in several models of acute pain as part of a multimodal analgesic plan (7). In our study, the occurrence of severe pain was reduced from 72% at baseline to 4.4% after 24 hours and 6.2% after 48 hours (Table 2).

Previous research on LDKI in POP analgesia has focused on analgesic efficacy and opioid consumption as primary outcomes (7,9). Trials included in systematic reviews of LDKI have tended to report hemodynamic changes as secondary outcomes. In these studies, it is possible that sampling was insufficiently powered for detecting hemodynamic changes. To the best of our knowledge, this is the largest observational study to report the cardiovascular response to LDKI in pain management.

Our study findings may be relevant for clinical practice. Previous research (8,13) has shown that ketamine alone as a single bolus or intraoperative infusions have failed to provide prolonged analgesia or prevent CPSP. Therefore, LDKI administered over several hours to days is recommended for treating severe POP in patients with high-intensity pain or at risk of CPSP (28,29). Benefits of LDKI in surgical analgesia have been particularly pronounced for thoracic, major orthopedic, and abdominal surgeries (6,30). Of particular interest, our data support the use of LDKI in patients with a history of HTN, as long as be adequately controlled. A relevant clinical finding in our study was the absence of an initial bolus dose of ketamine as part of a multimodal therapeutic intervention for treating acute pain. Previous studies (32,33) that included an initial bolus followed by LDKI reported no differences in cardiovascular side effects. Although an initial bolus followed by LDKI for 24-72 hours has been recommended previously, the effects of the therapy may be variable and treatment should depend on the judgment of the physician. Several systematic reviews of POP (7,25) have reported analgesic benefits of both modalities of LDKI (i.e., with and without an initial bolus).

**Limitations**

Limitations of the current study include the evaluation of patients with a stable general health status and exclusion of those with uncontrolled psychiatric or cardiovascular diseases. Future research should evaluate the effects of LDKI in patients with unstable HTN or elevated cardiovascular risk. Further, medication regi-

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### Table 5. Hemodynamic changes throughout the duration of ketamine infusion.

<table>
<thead>
<tr>
<th>Physiological Variable</th>
<th>Preinfusion (n=318)</th>
<th>24-h Infusion</th>
<th>48-h Infusion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (BPM), Me (IQR)</td>
<td>88 (77-100)</td>
<td>90 (78-103)</td>
<td>90 (78-100)</td>
<td>0.867</td>
</tr>
<tr>
<td>SAP (mmHg), Me (IQR)</td>
<td>122 (110-135)</td>
<td>123 (109-136)</td>
<td>123 (110-136)</td>
<td>0.551</td>
</tr>
<tr>
<td>DBP (mmHg), Me (IQR)</td>
<td>71 (64-77)</td>
<td>70 (63-78)</td>
<td>71 (63-77)</td>
<td>0.115</td>
</tr>
<tr>
<td>MAP (mmHg), Me (IQR)</td>
<td>88 (80-96)</td>
<td>87 (79-97)</td>
<td>88 (78-96)</td>
<td>0.505</td>
</tr>
</tbody>
</table>

*aFriedman test for dependent samples.

Abbreviations: HR, heart rate; BPM, beats per minute; Me, median; IQR, interquartile range; SAP, systolic arterial pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; h, hour; n, number.

### Table 6. Hemodynamic changes in patients with and without a history of HTN.

<table>
<thead>
<tr>
<th>Physiological Variable</th>
<th>HTN</th>
<th>No HTN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, Me (IQR)</td>
<td>129 (117-147)</td>
<td>119 (107-131)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>129 (114-144)</td>
<td>121 (109-133)</td>
<td></td>
</tr>
<tr>
<td>24-h infusion</td>
<td>130 (115-142)</td>
<td>121 (107-133)</td>
<td></td>
</tr>
<tr>
<td>48-h infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, Me (IQR)</td>
<td>71 (65.4-78.5)</td>
<td>70 (63-76)</td>
<td>0.714</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>71 (62-79)</td>
<td>70 (63-78)</td>
<td></td>
</tr>
<tr>
<td>24-h infusion</td>
<td>70 (65-78)</td>
<td>71 (63-77)</td>
<td></td>
</tr>
<tr>
<td>48-h infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, Me (IQR)</td>
<td>92 (82-101)</td>
<td>87 (78-96)</td>
<td>0.22</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>89 (79-99)</td>
<td>87 (79-96)</td>
<td></td>
</tr>
<tr>
<td>24-h infusion</td>
<td>91 (80-99)</td>
<td>88 (76-95)</td>
<td></td>
</tr>
<tr>
<td>48-h infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Kruskall–Wallis test.

Abbreviations: HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Me, median; IQR, interquartile range; h, hour.
mends and other medical comorbidities may alter cardiovascular responses to ketamine. Another limitation is that opioid consumption was not described in our study given the retrospective design. Opioid reduction with LDKI in acute pain has been previously described with a good level of evidence in a previous systematic review (9). Finally, we described only spontaneous reports of psychomimetic side effects for LDKI, since previous data support a low rate of central nervous system effects using a low-dose regime infusion, comparable to placebo.

**Conclusions**

Our retrospective evaluation of 318 patients treated for acute pain revealed LDKI administration (0.1 mg/kg/h) was not associated with significant hemodynamic changes. Our results support the more liberal use of LDKI for 24-72 hours when indicated as part of multimodal pain management.

**Acknowledgments**

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**References**


