

Low-dose Intravenous Ketamine for Postcardiac Surgery Pain: Effect on Opioid Consumption and the Incidence of Chronic Pain

Abstract

Background: Recent meta-analyses have concluded that low-dose intravenous ketamine infusions (LDKIs) during the postoperative period may help to decrease acute and chronic postoperative pain after major surgery. **Aims:** This study aims to evaluate the level of pain at least 3 months after surgery for patients treated with a postoperative LDKI versus patients who were not treated with a postoperative LDKI. **Methods:** Administrative and Ethics Board approval were obtained for this study. We performed a retrospective chart review for all patients receiving LDKI, and equal number of age-, sex-, and surgery-matched patients who did not receive LDKI. Low-dose ketamine was prepared using 100 mg of ketamine in 100 ml of normal saline and run between 50 and 200 mcg/kg/h. **Results:** We reviewed 115 patients with LDKI and 115 without LDKI. The average age was 63.1 years, 73% of the patients were men and sex was evenly distributed between LDKI and non-LDKI. The average duration of the ketamine infusions was 26.8 h with the average dose being 169.9 mg. At an average of 9 months after surgery, 42% of the ketamine group and 38% of the nonketamine group stated that they had had pain on discharge. Of these patients, 30% of the ketamine group and 26% of the nonketamine group still had pain at the time of the phone call. Women in both groups had more acute and chronic pain than men. **Conclusion:** These results show that LDKI does not promote a decrease in long-term postoperative pain.

Keywords: Cardiac surgery, chronic pain, ketamine

Introduction

Over the past two decades, many studies have been published on the effects of ketamine for postoperative pain. Several meta-analyses focusing on acute pain, perioperative pain in general, and thoracic pain in particular that have been published on this subject have concluded that low-dose intravenous ketamine infusions (LDKIs) during the postoperative period may help to relieve acute and chronic pain after major surgery, reduce the consumption of narcotics with only minimal side effects.^[1-6] Similarly, several randomized controlled trials (RCTs) have also noted decreased opioid consumption, decreased adverse effects as well as improved pain scores and satisfaction with LDKI.^[7-9] In cardiac surgery and the cardiac Intensive Care Unit (ICU), only one review has focused specifically on ketamine, without truly addressing its use for pain management.^[10]

Hypothesis

We hypothesized that patients receiving ketamine in the postoperative period would

consume less opioids and would have less chronic pain following cardiac surgery. Therefore, in our cardiac surgery specialized care center, some anesthesiologists used a low-dose ketamine infusion for all consecutive patients to whom they provided anesthesia with the intent of decreasing perioperative opioid consumption and the prevalence of postoperative chronic pain. This paper presents the results obtained and lessons learned from LDKI.

Methods

This case-control study combines a retrospective review of prospectively collected data and a prospective evaluation of chronic pain after surgery. Administrative and Ethics Committee approval was obtained: ICM-2011-1274.

Cases were defined as all patients >18 years of age, who had cardiac surgery involving a median sternotomy and who received an infusion of ketamine on arrival in the ICU. Controls were age-, sex-, and surgery-matched patients who did not

Jennifer Cogan,
Geneviève
Lalumière,
Grisell
Vargas-Schaffer¹,
Alain Deschamps,
Zeynep Yegin²

Departments of Anesthesia
and ²Nursing, Montreal
Heart Institute, Université
de Montréal, ¹Pain Center
of Hôtel-Dieu du CHUM,
Université de Montréal,
Montréal, QC, Canada

Address for correspondence:

Dr. Jennifer Cogan,
Montreal Heart Institute,
5000 Belanger, Montreal,
Quebec HIT 1C8, Canada.
E-mail: cogan.jennifer@me.com

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receive a ketamine infusion (–LDKI) in the postoperative period. The exclusion criteria included all patients for whom the standard extubation protocol was not applied and all patients in the nonketamine group who received enteral ketamine as an adjuvant pain medication in the postoperative period.

All patients, in both groups, received induction and maintenance anesthesia at the anesthesiologist's discretion and were administered the standard postoperative pain protocol, adjusted for individual needs by the acute pain team on a daily basis. LDKIs were prepared using 100 mg of ketamine in 100 ml of normal saline and infused at a rate between 50 and 200 mcg/kg/h for a maximum of 2 days.

Patients were contacted by phone between 6 and 13 months after their surgery by a research assistant to evaluate the prevalence of pain at the time of discharge (yes/no) and prevalence of surgery-related pain during the last 24 h (yes/no).

Descriptive results are presented as means \pm standard deviations for continuous variables and as frequencies (percentages) for categorical variables. Comparisons of demographics and clinical data at baseline were based on Student's *t*-tests for continuous variables and on Pearson's Chi-square statistics for categorical variables. The primary endpoint (pain postsurgery) was compared between groups. Statistical analysis was completed using SAS version 9.2 by the Montreal Health Innovations Coordinating Center.

Results

A total of 230 patients were included in the study, 115 who received low-dose postoperative ketamine (+LDKI) and 115 who did not receive low-dose postoperative ketamine (–LDKI). Follow-up response rates were 94.4% and 88.8% respectively for the ketamine and nonketamine groups. Descriptive analysis showed that there were no differences between the groups in terms of age, gender, weight, height, body mass index, American Society of Anesthesiologists status, type or length the surgery, and cardiac bypass time [Tables 1 and 2].

The average duration of the infusion was 26.8 h, the average dose was 169.9 mg, and the mean +LDKI dose in mcg/kg/h was 86.2 [Table 3]. Infusion of ketamine did not affect the length of intubation, the length of ICU or hospital stay but did show that patients required more opioid (morphine equivalents) in milligrams per kilogram before extubation [Table 4]. Table 5 presents intraoperative medications for both groups and Table 6 presents postoperative opioid consumption, in morphine equivalents, showing a slightly higher postoperative consumption of opioids in the ketamine group.

At follow-up, an average of 9 months after surgery, 47.8% of the (+LDKI) group and 44.6% of the (–LDKI) group stated that they had had pain on discharge. Of these

Table 1: Descriptive statistics of the study population for the (+LDKI) and (–LDKI) groups

	Ketamine	Non-Ketamine	P
Number of patients	115	115	1,0
Percent Male (<i>n</i>)	73,04 (84)	73,04 (84)	1,0
Mean Age (years)	63,1	63,0	0,925
Mean Weight (kg)	82,2	80,1	0,372
Mean Height (m)	1,7	1,7	0,899
Mean BMI (kg/m ²)	29,0	28,3	0,437
Type of Surgery % (<i>n</i>)			
CABG	51,30 (59)	52,17 (60)	NS
Valve replacement	20,87 (24)	24,35 (28)	NS
CABG + valve replacement	13,04 (15)	11,30 (13)	NS
Complex surgery	14,78 (17)	12,17 (14)	NS

Table 2: Intraoperative Information for the + LDKI and the –LDKI Groups

	Kétamine	Non Ketamine	P
Mean length of surgery (hours)	4,76	4,85	0,566
Mean length of cardiac bypass (hours)	1,37	1,37	0,984
Percent of patients with ASA score \geq 4	45,2	44,7	0,942
Percent of patients with a grade of intubation \geq 3	2,73	7,48	0,072

Table 3: Characteristics of + LDKI group

	Kétamine
Mean length + LDKI (hours)	26,8
Mean total dose of ketamine received (mg)	169,9
Mean + LDKI doses in mcg/kg/hours	86,2

Table 4: Length of intubation, length of ICU and hospital stay and postoperative morphine consumption for the + LDKI and –LDKI groups

	Ketamine	Non Ketamine	P
Length of intubation (hours)	9,69	8,60	0,079
MS Equiv ¹ prior to extubation (mg/kg)	0,39	0,29	0,005
Length of ICU stay (hours)	51,76	57,95	0,54
Length of hospital stay (days)	6,98	7,54	0,276

¹IV: Morphine Equivalents

patients, 37% of the (+LDKI) group and 33% of the (–LDKI) group still had pain at the time of the phone call [Tables 7 and 8]. Neither of these differences was statically significant. However, a significantly higher proportion of women in both the (+LDKI) and (–LDKI) group complained of pain on discharge and chronic pain, at the time of the phone call [Tables 7 and 8].

Discussion

This case–control study evaluates the prevalence of chronic pain at an average of 9 months' postcardiac surgery in two

groups of patients: Those who received ketamine and those who did not. The results do not demonstrate that ketamine infusion decreased the level of opioid consumption nor chronic postoperative pain. Ketamine infusions did not result in a lower proportion of patients complaining of pain between 6 and 12 months after surgery, nor did it have an impact at the time of discharge as patients in the ketamine group recalled slightly higher levels of pain at the time of discharge than those who did not receive ketamine. What is compelling, however, is that women report pain at discharge (approximately, 65% in both groups) and long-term (approximately 50% in both groups) than men. This difference is statistically significant.

It is interesting to note that although most published RCT's and meta-analysis studies, including those referenced above, show a modest positive effect for ketamine as a perioperative analgesic none have evaluated the influence of ketamine on the prevalence of chronic pain. This study provides evidence in real-life anesthesia that a postoperative

ketamine infusion was not effective in decreasing chronic pain after cardiac surgery. This real-world effectiveness study is the first to evaluate the potential long-term benefits of ketamine for decreasing chronic postoperative pain after cardiac surgery.

Of note is that narcotic consumption in the postoperative period was significantly higher in the +LDKI group. This may be because anesthesiologists who administered an LDKI postoperatively also tended to use higher doses of intraoperative opioid when compared to all comers in the non-LDKI group. This raises the question of whether or not hyperalgesia or some other postoperative pain protocol factor could be a contributing to the higher doses of narcotics seen postoperatively in the +LDKI group. Although some studies have indicated that high dose opioids are a factor in postoperative hyperalgesia most implicate remifentanyl. Few human data are available with respect to more long-acting opioids.^[11]

This study demonstrates the effectiveness, as opposed to the efficacy, of a systematically applied technique in a real-world clinical situation.^[12] Evaluation of the data showed that the technique was not effective in decreasing postoperative pain and consequently led the investigators to cease application of the technique. One hypothesis for these results is that the lack of postoperative effectiveness may have been related to the fact that both groups received intraoperative ketamine. An intraoperative dose of ketamine may be all that is required to provide a decrease in postoperative pain and adding a continuous infusion provides no added benefit.

One weakness of this study is the lack of prospective data for pain scores at discharge as it is possible that there is a recall bias related to the level of pain experienced by patients after surgery. This is somewhat tempered by prospectively collected chronic pain scores.

Conclusion

In a real-world, effectiveness study, low-dose intravenous ketamine (+LDKI) for post cardiac surgery pain did not result in a decreased incidence of chronic pain. A significantly large number of patients, women, in

Table 5: Mean Doses of Medications for the +LDKI and -LDKI groups

Type of Medication	Ketamine	Non Ketamine	P
Intraoperative MS Equiv ¹ (mg)	299,0	248,3	<0,001
Intraoperative MS Equiv ¹ (mg/kg/h)	8145	651,3	<0,001
Intraoperative Ketamine (mg)	57,9	41,8	<0,001
Intraoperative Magnesium (mg)	3195,9	2596,9	0,06
Preoperative Gabapentin (mg)	507,0	370,4	0,019
Preoperative Acetaminophen (mg)	761,3	469,0	<0,001

¹ MS: IV Morphine Equivalents

Table 6: Postoperative Narcotic Consumption (mg/kg/day) on days 0 to 4

Postoperative Day	Ketamine	Non Ketamine	P
MS Equiv ¹ Day 0 (mg/kg)	0,42	0,38	0,053
MS Equiv ¹ Day 1 (mg/kg)	0,49	0,42	0,004
MS Equiv ¹ Day 2 (mg/kg)	0,29	0,26	0,055
MS Equiv ¹ Day 3 (mg/kg)	0,11	0,08	0,023
MS Equiv ¹ Day 4 (mg/kg)	0,08	0,04	0,027

¹ IV: Morphine Equivalents

Table 7: Proportion of patients in the -LDKI group who had pain at discharge and at the time of phone call

Demographics	Pain at discharge %	Pain at time of phone call %	Pain on discharge/pain at average 9 months post surgery %
Males	33.8	26.4	78.1
Females	70.0	48.3	69.0
Total	43.6	32.7	75.0

Table 8: Proportion of patients in the +LDKI group who had pain at discharge and at the time of phone call

Demographics	Pain at discharge %	Pain at time of phone call %	Pain on discharge/pain at average 9 months post surgery %
Males	40.7	32.1	78.8
Females	67.9	46.4	68.3
Total	47.7	35.8	75

particular, are at high risk for long-term pain after cardiac surgery. Measures such as daily individualized patient care plan closely monitored and tailored analgesic regimens and special attention to women undergoing surgery need to be implemented to decrease the burden chronic pain after cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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