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Ketamine Decreases Postoperative Pain Scores in Patients Taking Opioids for Chronic Pain: Results of a Prospective, Randomized, Double-Blind Study

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Abstract

Background. Patients prescribed opioids for chronic pain may suffer from inadequate postoperative pain control. Ketamine is an adjuvant demonstrating analgesic and opioid-sparing effects. We

hypothesize that an intravenous ketamine infusion in addition to opioid-based patient-controlled analgesia (PCA) improves postoperative pain relief in this patient population.

Methods. We evaluated 64 patients with chronic pain taking opioids undergoing nononcologic surgery. Patients were randomized to receive either postoperative hydromorphone PCA and continuous ketamine (0.2 mg/kg/hour), or hydromorphone PCA and saline. Patients provided numeric rating scale (NRS) pain scores for "worst," "average," and "least" pain following surgery. The primary outcome measure was change in patients' postoperative NRS scores compared with baseline NRS. Secondary and tertiary outcomes included postoperative day one 24-hour opioid use and the amount of opioid used 24 hours prior to hospital discharge.

Results. Fifty-nine patients were included in the analysis. Baseline patient characteristics were similar with the exception of age. Patients using ketamine had decreased "average" pain scores (percent change between postoperative and preoperative NRS) after surgery (13.5% decrease in the ketamine group vs 15.5% increase in NRS in the placebo group, $P = 0.0057$). There were no differences in "worst" or "least" pain scores or postoperative opioid use. Side effects between groups were similar.

Conclusions. Our study demonstrates that a postoperative ketamine infusion at 0.2 mg/kg/hour in addition to opioids results in a statistically significant reduction of "average" pain scores in patients undergoing surgery who take opioids for chronic pain. However, "least" and "worst" pain scores and the amount of opioid used postoperatively did not differ between groups. Thus, the use of a postoperative ketamine infusion at 0.2 mg/kg/hour provides limited benefit in improving pain management for this challenging population.

Key Words. Ketamine; Postoperative Pain; Chronic Opioid; Chronic Pain

Introduction

Although significant advances have been made in managing postoperative pain starting with the advent of patient-controlled analgesia (PCA) in the 1970s, there remain subset populations of patients who continue to have poorly managed pain after surgery. With the increase in prescribing of opioids for chronic noncancer pain, there is now a large population of patients who are likely tolerant to the analgesic effects of opioids. Inevitably, many of those patients may eventually need surgical interventions.

Studies have shown that tolerance to opioids and a decreased pain threshold may persist even long after opioids have been discontinued [1,2]. In addition to tolerance, patients may demonstrate increased pain sensitivity or opioid-induced hyperalgesia resulting from chronic opioid use [3,4]. Patients may have either a higher requirement for opioids or may appear to be "resistant" to their effects—and, therefore, may suffer from poorly managed or uncontrollable pain after an operation.

A common strategy is to offer such patients higher doses of opioids to overcome their presumed tolerance. However, this approach may result in the development of unacceptable opioid-related side effects, including excessive sedation, bowel dysmotility, and possibly a state of opioid-induced hyperalgesia in which pain actually worsens as higher doses of opioids are given. Multimodal postoperative pain treatment strategies in patients taking opioids for chronic pain are therefore paramount to successful recovery and prevention of undesirable clinical outcomes [5].

Ketamine, an *N*-methyl-$_D$-aspartate (NMDA) receptor antagonist, has been widely studied as an analgesic adjuvant when administered in subanesthetic doses to opioid-naïve patients. Ketamine use has been associated with decreased opioid requirements after surgery, decreased opioid-induced side effects such as nausea and vomiting, and may prevent the development of chronic pain and hyperalgesia [1,6–11]. Both tolerance and hyperalgesia are known to be mediated by the NMDA receptor [12]. Providing NMDA receptor antagonist drugs may reduce tolerance and confer better pain relief for patients who take opioids chronically and who need opioids for postoperative pain relief. Although opioids remain the primary method of providing systemic analgesia after major surgery, the use of ketamine may result in improved analgesia compared with that of opioids alone, especially for the opioid-tolerant population.

Several studies have examined the use of perioperative ketamine in patients taking long-term opioids for chronic pain [13–15]. Study designs, definitions of chronic opioid use, ketamine doses, and administration schedules were quite variable. Only one study found a significant opioid-sparing effect of ketamine, and in this study ketamine was administered only intraoperatively [14]. There is no established dose or recommended timing of administration of perioperative intravenous (IV) ketamine. We hypothesized that providing a postoperative ketamine infusion at 0.2 mg/kg/hour to opioid-dependent chronic pain patients undergoing nononcologic surgery would decrease postoperative pain scores in the initial 24 hours. Secondary and tertiary outcomes evaluated included the amount of opioid used 24 hours postoperatively and 24 hours prior to hospital discharge in comparison to baseline use.

Methods

General Description

This study was approved by the Partners Human Research Committee in Boston, Massachusetts. Written

informed consent was obtained from all subjects. This was a prospective, randomized, double-blind study investigating the effect of a postoperative ketamine infusion in patients with chronic pain managed with opioids preoperatively.

The study was performed from September 2008 to June 2011. Patients eligible for enrollment were adults scheduled for hospital admission after major surgery, which was defined as surgery that leads to inpatient hospitalization and use of IV PCA with opioids. Patients were included if they were taking opioids for chronic pain, with patients having moderate to severe pain in the absence of acute tissue damage for at least 3 months prior to enrollment. Long-term opioid use was defined as ≥1 month of opioid therapy at doses of oral morphine ≥60 mg/24 hours, oxycodone ≥30 mg/24 hours, or hydromorphone ≥8 mg/24 hours, or an equianalgesic dose of another opioid. Patients were excluded from study participation if they had chronic pain due to metastatic or locally invasive cancer, a primary cancer diagnosis, evidence of psychosis, pregnant women, and patients with an altered mental status that would make the subject unable to complete outcome questionnaires. We also excluded patients who were given regional anesthesia intraoperatively or postoperatively, as well as patients who were taking methadone. Patients taking methadone were excluded from eligibility because of this drug's NMDA receptor antagonistic properties so as to not confound the potential results of administering ketamine.

Subject Enrollment

Potential subjects were identified through the electronic database of the Weiner Center for Preoperative Evaluation at Brigham and Women's Hospital (BWH). Information about the study was made available to participating surgeons who were notified about subject eligibility so that a preoperative discussion regarding the study could be conducted. Investigators reviewed the study parameters, and inclusion and exclusion criteria with patients during their routine preoperative evaluation prior to anticipated major surgery. If eligible, patients were offered the option to participate in the study, and informed consent was obtained.

Study Procedures and Design

Subjects completed a baseline demographic questionnaire. Baseline preoperative pain numeric rating scale (NRS) scores (worst, least, and average) were obtained. In addition, the following baseline measurements were obtained: Hospital Anxiety and Depression Scale (HADS), symptoms checklist, and medication side effects questionnaire. The BWH Investigational Drug Service (IDS) randomized subjects to two groups for pain control after surgery: one group who received IV hydromorphone PCA plus an IV ketamine (0.2 mg/kg/hour) infusion, and the other who received hydromorphone PCA plus an IV placebo (normal saline) infusion. In the intraoperative period, subjects received either general anesthesia with an inhalational anesthetic or, if neuromonitoring was required by the surgeon, a total IV anesthetic (TIVA) with propofol and remifentanil. Intraoperative anesthetic management and choice of drugs was at the discretion of the anesthesiologist. Patients received IV opioid (hydromorphone or fentanyl) as part of their routine anesthetic management, with dosages determined by the anesthesiologist assigned to their case. The doses of IV opioid used were documented as part of our study analysis. Ketamine was not administered intraoperatively.

Ketamine or saline placebo infusions were prepared by IDS and labeled as ketamine/placebo. On arrival to the postanesthesia care unit (PACU), all subjects were given hydromorphone PCA with settings allowing an administration of hydromorphone between 0.2 and 0.5 mg IV every 7 minutes as needed. Rescue doses were allowed per standard protocol based on nursing assessment and patient request (e.g., 0.5 mg IV every 5 minutes × 3 doses). In the PACU, concurrent with the initiation of the hydromorphone PCA, subjects were given the study drug, either a ketamine infusion at 0.2 mg/kg/hour or placebo at an equivalent rate. Subjects, nurses, and physicians involved in the subjects' care were blinded to whether the patient was receiving ketamine or placebo. Subjects were managed for pain control by the Acute Post-Operative Pain Management Service (APOPS) or study personnel until they were transitioned to oral therapy, typically on the morning of postoperative day one. Subjects who felt that their pain relief was inadequate postoperatively were able to have their PCA demand dose increased by up to 50% every hour to a maximum of two dose increases. If after two PCA adjustments subjects continued to have poorly controlled pain, or if they rated their pain as "severe" on the categorical rating of pain intensity scale, subjects were unblinded and removed from the study. Subjects were also unblinded if at any point the patient reported intolerable side effects from treatment and/or wished to be unblinded. For patients who were unblinded, subsequent analgesic management was provided as deemed appropriate by APOPS, including the option to continue IV PCA and/or ketamine, or to begin an infusion of ketamine if the patient had been receiving placebo. The reason for unblinding subjects was documented.

The following measurements were taken once per day on morning rounds by APOPS or study personnel: worst, least, and average pain scores for the preceding 24 hours (0–10 NRS); categorical rating of pain intensity; analgesic consumption (total milligrams of hydromorphone plus other home or oral opioid used per 24 hours); total use of study drug infusion per 24 hours; types and doses of other drugs required for pain relief; adverse events scales and checklist including a nausea scale (0 = absent, 1 = present, no therapy, 2 = present, therapy effective, 3 = present, therapy ineffective), pruritis scale (0 = absent, 1 = present, no therapy, 2 = present, therapy effective, 3 = present, therapy ineffective), respiratory depression (number of instances per 24 hours of RR < 8 or SpO2 < 90%), sedation level (modified Ramsey scale: 1 = anxious, 2 = cooperative/oriented, 3 = responds to

commands, 4 = brisk response to stimulus, 5 = sluggish response to stimulus, 6 = no response to stimulus), and presence of disturbing dreams or hallucinations; and any medication side effects (per side effects checklist).

At the conclusion of the study (when IV analgesics were discontinued or when a subject was unblinded), a Treatment Helpfulness Questionnaire and Satisfaction Questionnaire were also obtained. Additional data such as surgical time, surgical procedure performed, and total opioid use in the 24 hours prior to discharge were collected by chart review.

Power and Statistical Analysis

We tested our primary, secondary, and tertiary hypotheses: that ketamine would improve pain relief (greater beneficial change in NRS scores in patients receiving ketamine compared to placebo), that ketamine would result in lower opioid use during hospitalization, and that ketamine would result in prescribing of lower opioid amounts on discharge.

Sample Size and Power Calculations

From published literature, in this patient population, the mean NRS score for chronic pain (average pain) is assumed to be 6.0, with a standard deviation of 1.8. NRS scores for current pain, highest pain, and lowest pain were also estimated based on literature review of this type of patient population. Sample size calculations were based on a two-tailed two-sample (difference of two-point reduction in NRS after institution of ketamine treatment vs placebo) Student's *t*-test. The type I error (α, significance level) is fixed to be 5%, while the type II error (β, 1-statistical power) is fixed to be 90%. In order to detect a two-point reduction in the mean NRS score, a total of N = 38 patients were required (i.e., N = 19 per each study arm). To allow for potential dropout of subjects during the study and to facilitate multivariate analysis, we recruited 64 patients into the study.

Statistical Analysis

The primary analysis comparing demographic information, pain scores, and opioid use between the two groups was done using Wilcoxon rank sum test, and categorical outcomes were compared using the chi-squared test or Fisher's exact test as appropriate. To evaluate potential confounding covariates, a multivariate regression approach was performed. Results of the analysis were presented using 95% confidence intervals, and a *P* value of <0.05 was indicative of statistical significance. Data analysis was done using SAS version 9.3 software (Statistical Analysis System, Cary, NC, USA).

Results

Using the patient visit list of the BWH preoperative testing center, 72 patients were identified consecutively as eligible for enrollment and approached for study inclusion. Of these, eight patients either were not interested in the study or their planned surgery was canceled. Thus, 64 patients consented and were randomized to one of the two treatment arms. Of these, 59 patients completed the study, and their data were used for analysis. Of the five patients who were excluded, two patients opted to have a morphine PCA, and three patients were discharged earlier than anticipated on postoperative day one and prior to their first scheduled study data collection time point. Unblinding occurred in eight patients during the study: two patients requested unblinding secondary to "anxiety"—one had received ketamine and the other placebo; 4 of 29 patients receiving placebo were unblinded secondary to pain vs 1 of 30 patients receiving ketamine; and one patient receiving placebo was unblinded secondary to respiratory depression (Figure 1).

There were no significant differences between patients who received ketamine compared with those who received placebo based on gender, height and weight, American Society of Anesthesiologists (ASA) class, preoperative opioid analgesic use, the HADS, and level of preoperative chronic pain (least, average, and worst NRS). However, the group randomized to receive ketamine was somewhat younger in age than those who received placebo (48.5 $\pm$ 11.9 years vs 55 $\pm$ 11.2 years, respectively, $P = 0.02$) (Table 1).

Patients had similar intraoperative anesthetic management. All patients received either general anesthesia with an inhalational agent, or a TIVA with propofol and remifentanil. Both modalities were supplemented by IV fentanyl or hydromorphone. The number of patients who received remifentanil was equally distributed among groups. In addition, there were no differences between the two study groups in the type or duration of surgery (Table 2).

Patients reported "worst," "least," and "average" postoperative pain scores. When the differences between postoperative and preoperative pain scores were evaluated, there was a statistically significant benefit noted for patients who received IV ketamine compared with those who received placebo in "average pain" scores (Table 3). This effect persisted when adjusting for patient age. No significant differences were noted among "least" and "worst" pain measures.

There were no differences between the two groups in the length of hospital stay, the duration of the infusion, the total consumption of opioid when converted to oral morphine equivalents 24 hours postoperatively, and the total consumption of morphine equivalents 24 hours prior to discharge (Table 4). Also, there were no differences between groups in the ratio of postoperative opioid doses to home preoperative opioid doses, either when considering the initial 24-hour postoperative dose or the 24 hours prior to discharge dose (Table 4). There were no differences noted between groups in terms of preoperative medication side effects (data not shown) or treatment-related adverse events during the first 24 hours after surgery (Table 5). Administering a ketamine infusion at this

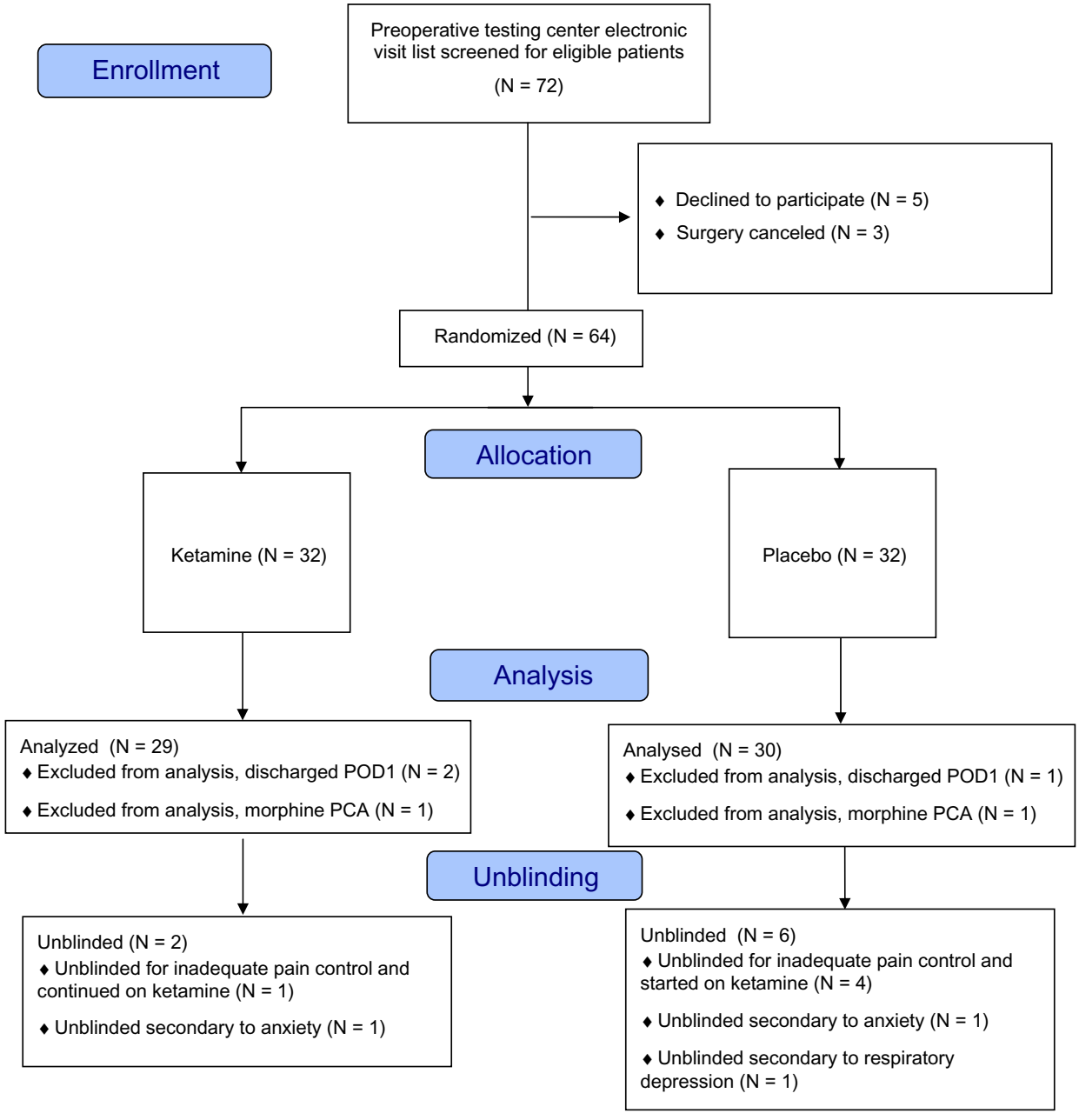

Figure 1 Enrollment flow diagram. PCA = patient-controlled analgesia; POD1 = postoperative day 1.

dose (0.2 mg/kg/hour) was not associated with adverse hemodynamic changes or with noticeable cognitive-behavioral changes.

A multivariate linear regression model was used to evaluate if there were any potentially confounding factors or whether certain subgroups of patients had outcomes that were not those of the mean. Plots did not indicate any differences between outcomes based on patient age, gender, height and weight, surgical time, ASA status, type of surgery, depression and anxiety scores, levels of sedation or other side effects, or overall levels of preoperative opioid consumption. There was no difference in the estimated effect of ketamine based on any of these parameters with the covariate-adjusted model, including age, which was significantly different between groups on univariate analysis.

Subgroup analysis was performed to investigate the effect of the level of preoperative opioid use on the outcome variables. Patients were categorized into a higher morphine group (morphine equivalents ≥200 mg/day

Table 1 Preoperative demographics

Variable	Ketamine (N = 29) (%)	Placebo (N = 30) (%)	*P* value
Age			0.0238
Years (mean ± SD)	48.5 ± 11.9	55 ± 11.2	
Sex			0.9080
Male	13 (22.0)	13 (22.0)	
Female	16 (27.1)	17 (28.8)	
Height			0.8123
Inches (mean ± SD)	66.6 ± 3.8	66.9 ± 5.1	
Weight			0.5739
Kg (mean ± SD)	77.5 ± 22.8	80.5 ± 17.0	
Morphine category			0.8502
<200 mg/day	20	20	
≥200 mg/day	9	10	
HADS (depression)			0.7948
Median score (interquartile range)	8.5 (5–13)	8 (5–11)	
HADS (anxiety)			0.4972
Median score (interquartile range)	9 (5.5–13.5)	8.5 (5–11)	
Pre-op worst pain			0.4877
Score (mean ± SD)	9.3 ± 1.5	9.5 ± 0.8	
Pre-op least pain			0.8795
Score (mean ± SD)	4.2 ± 2.2	4.3 ± 2.4	
Pre-op average pain			0.7485
Score (mean ± SD)	6.7 ± 2.0	6.5 ± 1.7	

HADS = Hospital Anxiety and Depression Scale.

Table 2 Operative characteristics

Variable	Ketamine (N = 29) (%)	Placebo (N = 30) (%)	*P* value
Surgical time			0.6279
Hours (mean ± SD)	2.7 ± 0.9	2.6 ± 1.0	
ASA class Physical Status Classification System			0.7847
1	1 (1.7)	0 (0)	
2	19 (32.2)	19 (32.2)	
3	9 (15.3)	11 (18.6)	
Surgery type			0.3609
Lumbar/thoracic	18 (62)	21 (70)	
Cervical	1 (3)	4 (13)	
Hip	8 (28)	4 (13)	
Upper/lower extremity	1 (3)	0 (0)	
Abdominal	1 (3)	1 (3)	
Intraoperative opioid use			
Intravenous hydromorphone (mg)	3.7 ± 2.6	2.7 ± 1.9	0.1062
Intravenous fentanyl (mcg) (mean ± SD)	285.3 ± 173.1	340.0 ± 526.1	0.5967
Remifentanil infusion			0.9475
Yes (i.e., total intravenous anesthetic)	6 (10.2)	6 (10.2)	
No (i.e., inhalational anesthetic)	23 (39.0)	24 (40.7)	
Remifentanil bolus			0.7469
Yes	4 (6.8)	5 (8.5)	
No	25 (42.4)	25 (42.4)	

ASA = American Society of Anesthesiologists.

Table 3 Postoperative pain scores for "worst," "least," and "average" pain

	Ketamine (N = 29)	Placebo (N = 30)	*P* value
Postoperative pain scores (NRS 0–10)			
Pain worst	8.7 ± 2.0	9.0 ± 1.9	0.4102
Pain least	4.4 ± 3.1	5.6 ± 3.0	0.1085
Pain average	6.0 ± 2.2	7.3 ± 2.2	0.0241
Change in postoperative vs preoperative pain scores			
Δ Pain worst	–0.6 ± 1.9	–0.6 ± 1.7	0.93
Δ Pain least	0.2 ± 2.7	1.3 ± 2.9	0.15
Δ Pain average	–0.6 ± 1.9	0.8 ± 2.2	0.0135
Percent (%) change in postoperative vs preoperative pain scores			
% Δ Pain worst	–8.2 ± 2.7%	–6.1 ± 19%	0.95
% Δ Pain least	2.3 ± 64%	26.1 ± 64%	0.19
% Δ Pain average	–13.5 ± 37%	15.5 ± 42%	0.0057

NRS = numeric rating score.

[N = 19]) and a lower morphine group (morphine equivalents <200 mg/day [N = 40]). Regardless of their preoperative morphine-equivalent dose category, patients given ketamine had an improvement in percent change "average pain" compared with the placebo group ($P = 0.048$ in the ≥200 mg/day group, $P = 0.05$ in the <200 mg/day group). There was no difference in postoperative percent change in least or worst pain scores, or in the ratio of 24-hour postoperative to preoperative opioid use, and in the ratio of 24 hours prior to discharge opioid use to preoperative opioid use.

Discussion

We have demonstrated that a postoperative IV ketamine infusion can improve average pain scores in patients who receive moderate to high doses of opioids for chronic pain and who then undergo surgery. However, although our analysis achieved statistical significance, we observed only a 1.3-point reduction in "average" pain scores in the ketamine group vs placebo, and there was no difference in "least" and "worst" pain scores. In addition, the dose of ketamine we used did not reduce overall opioid consumption postoperatively. We demonstrated that there are no meaningful adverse effects of infusing ketamine 0.2 mg/kg/hour to patients in the immediate postoperative period. Although our results are modest, our findings provide clinical support to the basic science literature and human studies on ketamine, which suggests that the use of an NMDA receptor antagonist may potentiate opioid analgesia, decrease hyperalgesia, and reduce tolerance to opioids [6,9,10,16].

In our sample, we did not find any preoperative characteristics to affect whether a patient taking long-term opioids responds better or worse to an IV ketamine infusion after surgery. One of the challenges of studying efficacy of a treatment in patients with severe chronic pain is that measuring the additional contribution to pain scores from postoperative pain can be problematic when the baseline chronic pain scores are already elevated. Because many of the patients in this study had "worst pain" preoperative levels that were rated 10/10 on the NRS scale, it was difficult to assess outcomes in this group as an increase of pain after surgery would still be reported as a 10/10 score. It was in the category of

Table 4 Postoperative characteristics and opioid use

Variable	Ketamine (N = 29)	Placebo (N = 30)	*P* value
Duration of infusion (hours)	19.5 ± 5.1	17.8 ± 3.4	0.1364
Hospital length of stay (days)	4.8 ± 1.07	5.2 ± 2.09	0.3917
Patient's satisfaction (0–10 scale, 10 representing higher satisfaction)	6.8 ± 3.1	7.0 ± 3.2	0.8131
Treatment helpfulness (0–10 scale, 10 representing highest perceived helpfulness)	7.3 ± 2.6	7.2 ± 1.9	0.9808
24-hour post-op opioid use (oral morphine equivalents)	726 ± 489	770 ± 560	0.7480
24-hour prior to discharge opioid use (oral morphine equivalents)	344 ± 238	392 ± 380	0.5584
Ratio of 24-hour post-op to home pre-op opioid use	6.1 ± 3.5	7.0 ± 4.5	0.6062
Ratio of 24-hour prior to discharge to home pre-op opioid use	2.5 ± 1.6	2.9 ± 2.6	0.7617

Table 5 Treatment related adverse events

Variable	Ketamine N (%)	Placebo N (%)	*P* value
Respiratory depression			0.5091
Yes	0	1 (1.8)	
No	27 (49.1)	27 (49.1)	
Hallucination			0.4909
Yes	1 (1.8)	0	
No	26 (47.3)	28 (50.9)	
Pruritis (scale 0–3)			0.0953
0	22 (40)	26 (47.3)	
1	4 (7.3)	0	
2	1 (1.8)	1 (1.8)	
3	0	1 (1.8)	
Sedation (scale 0–6)			0.2457
Mean ± SD	1.8 ± 0.8	2.1 ± 1.2	
Median, range	2 (0–3)	2 (0–5)	
Nausea (scale 0–3)			0.5403
Mean ± SD	0.5 ± 0.9	0.3 ± 0.8	
Median, (IQR)	0 (0–3)	0 (0–3)	

IQR = interquartile range.

"average pain" that scores were the most improved with ketamine infusions. However, it is important to note that our results, while statistically significant, did not meet the original criteria we used for determining the sample size for the study, which were based on our initial hypothesis of finding a two-point reduction in NRS between groups. We observed a 1.3-point difference in "average pain" between groups.

In order to determine factors that may have a role in the effect of ketamine on postoperative pain and opioid consumption, we attempted to stratify patients based on the amount of preoperative opioid each patient used. Although we defined eligibility for the study as long-term opioid use of at least 60 mg orally of daily morphine or its equivalent, our patients' preoperative morphine equivalent use was as high as 550 mg per day. Subgroup analysis of patients taking lower doses of morphine at <200 mg/day compared with those taking higher doses of morphine at ≥200 mg/day did not demonstrate a significant difference in our outcome variables. A larger sample size of patients in both high- and low-dose opioid groups would be needed to substantiate these results, and our study was not powered to examine this. Within our study patient population, we did not identify any particular subsets of patients who may have better outcomes based on the use of ketamine.

A number of other studies have been published evaluating the use of ketamine in opioid-dependent populations undergoing surgery [13–15]. In these studies, baseline levels of opioid use, ketamine doses and timing of administration, anesthetic management, and postoperative effects of ketamine varied. Loftus et al. found a significant effect of IV ketamine in opioid-dependent surgical patients who were administered IV ketamine *intraoperatively*, but patients were not given ketamine postoperatively in this study. Studies of opioid-naïve patients have found there may be a "preventive analgesia" effect when ketamine is given prior to injury or surgical incision [17]. The use of IV ketamine given as a 0.25–0.5 mg/kg bolus before surgical incision followed by an infusion 0.2–0.5 mg/kg/hour for 24 hours has been suggested [9].

The long-term effect of administering ketamine perioperatively to opioid-naïve patients demonstrates conflicting data on the prevention of chronic postsurgical pain [18,19]. It is possible that a higher dose ketamine regimen may have an opioid-sparing effect that not only translates to lower opioid consumption for patients in the immediate postoperative period, but in overall lower opioid consumption in the long term [14]. It could be postulated that if ketamine use decreases opioid consumption in the postoperative period, there may be an overall lessening of opioid hyperalgesia in these patients. Therefore, the use of ketamine perioperatively may be a method to reduce the dosage of long-term opioids taken by patients with chronic pain. We did not analyze pain and opioid use after hospital discharge, but further study should be done to evaluate for this potentially attractive outcome. Future studies are also needed to evaluate a dose response and side effects profile for various doses of ketamine when given to patients who use long-term opioids for chronic pain.

Our study has the following limitations: 1) our study design was based on the clinical practice in our hospital of using ketamine postoperatively for a broad range of surgical patients. Therefore, patients were not homogeneous in their reasons for surgery, and we enrolled patients who underwent different types of surgical procedures. We did not stratify patients based on their underlying diagnosis causing chronic pain, whether their postoperative pain was mostly nociceptive or neuropathic, or if their pain severity was influenced by the type of surgery they underwent. This variability of our patients and their surgery types may have confounded our results. 2) We did not power our study to evaluate results based on the amount of opioid consumed by patients on a long-term basis. Our patients were taking variable opioid doses for chronic pain. More rigid inclusion criteria to limit the range of opioid use could have improved the standardization of results. 3) Our study did not control intraoperative anesthetic management and included inhalational anesthetics or TIVA with remifentanil if neuromonitoring during spine surgery was required. Remifentanil-induced hyperalgesia and tolerance has been well documented, and the use of remifentanil may have an effect on the impact of ketamine on hyperalgesia and tolerance [20–22]. Our study was not designed to evaluate the impact of this variable on outcomes of ketamine infusions; however, the number of patients who received remifentanil was small and equally distributed among treatment groups. 4) The length of administration of the ketamine/placebo infusions was not standardized in our study as the transition from IV to oral

analgesia was determined by clinical factors. Typically, patients were transitioned to a per os (PO) regimen on postoperative day one (about 18 hours after surgery) as deemed appropriate, although some patients in our study continued to receive IV ketamine/placebo until postoperative day 2. 5) We recorded pain scores at only one time point on each postoperative day and did not measure pain scores after the ketamine infusion was discontinued. Having more data points may have provided additional useful information on patient outcomes. In addition, measurement of pain scores beyond the length of the infusion should be studied in the future. 6) Other secondary measures of pain, such as pain with movement and quality of sleep, were not collected.

Our study reflects the actual clinical practice in our institution and provides information on the postoperative use of ketamine in a general population of surgical patients who take opioids for chronic pain. Future studies with larger patient cohorts may be able to distinguish the relative contribution of the earlier-noted variables on outcomes.

Conclusion

We have evaluated the efficacy of IV ketamine in addition to IV hydromorphone administered postoperatively to patients who take moderate to high doses of opioids for chronic pain and who undergo surgery. Our study demonstrates that a ketamine infusion at 0.2 mg/kg/hour in addition to IV PCA results in a statistically significant improvement in postoperative "average" pain scores in this population. We did not find differences in "least" or "worst" pain scores in patients receiving ketamine or placebo. Additionally, the differences in "average" pain scores between the ketamine and nonketamine groups were modest, with a difference in NRS of 1.3 favoring the ketamine group.

Therefore, while a statistically significant difference was noted in postoperative "average" pain scores between groups, no clinically significant differences were noted in any group based on the defined primary outcome, which was a two-point change in the NRS score. It is important to note that our study has a number of methodological considerations that may limit the applicability of these findings. Additional studies need to be conducted to determine the optimal patient and surgical variables for using perioperative ketamine, as well as the best dose and timing of perioperative ketamine that are both safe and effective for patients with chronic pain who take long-term opioids.

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