Anesthesiology 2010; 113:514–5

Ketamine for Managing Perioperative Pain in Opioid-dependent Patients with Chronic Pain

A Unique Indication?

IN this issue of ANESTHESIOLOGY, Loftus *et al.*[1] report findings from a study examining the utility of ketamine as an adjunct analgesic in controlling postoperative pain. Is this just another report on the perioperative use of ketamine addressing a question that has already been answered? We know this works, right? Considering that the population under study consisted of patients on long-term opioid therapy for chronic pain, the report may be worth a closer look.

The use of opioids for the control of chronic pain is now commonplace. Opioid prescriptions increased greatly over the past decade, hydrocodone/acetaminophen being the most commonly prescribed drug in the United States for the past several years by a substantial margin.[2–5] Once the province of the pain specialist, long-term opioid prescribing is now in the repertoire of most primary care physicians, and virtually all chronic pain management guidelines endorse the use of opioids at some point in chronic pain treatment algorithms. Few data are readily available to address quantitatively the assertion that an increasing percentage of patients receiving opioids, particularly in large amounts, come to our operating rooms for all types of surgeries, but it seems undeniable.

There is widespread belief among clinicians that patients receiving long-term opioid therapy present significant perioperative management problems. For example, opioid requirements are often greatly increased (on average about three times those of opioid-naive patients), although prediction of postoperative opioid needs for individual patients remains difficult.[6–8] Some have found postoperative pain scores to be worse despite the availability of acute pain management experts.[8] Perhaps most worrisome, but not well studied, is the notion that the therapeutic index of opioids might be narrowed, making these patients particularly vulnerable to serious side effects or inadequate pain control. Finally, opioid doses tend to be substantially higher, compared with preoperative levels, at the time of discharge from hospital. Dose reduction in this setting can be a complex undertaking. Although the real impact of these challenges remains uncertain, several authors have offered their opinions concerning how patients receiving long-term opioid therapy should be managed.[9–12] Most often, the interrelated opioid "maladaptations" of tolerance, opioid-induced hyperalgesia, and physical dependence are cited as the roots of specific management problems.

If we accept that patients receiving long-term opioid therapy are a population of special concern, we might then ask how we would rationally improve their postoperative pain management. Setting aside regional anesthesia, our analgesic trump card, we might opt to use adjunctive analgesics that would both reduce the impact of long-term opioid consumption and contribute to analgesia *via* opioid-independent mechanisms. An ideal drug would reduce opioid tolerance, would attenuate opioid-induced hyperalgesia, and would have proven analgesic properties of its own. Ketamine and perhaps α-2 agonists such as dexmedetomidine may fill the bill. Both ketamine and dexmedetomidine have been advocated as adjuvants in the analgesic management of patients receiving long-term opioid therapy, although there are few data yet to support those recommendations.

The basic and clinical pharmacology of ketamine have been well studied. Although it has many potential sites of action, its *N*-methyl-D-aspartate receptor blocking properties are most frequently discussed. A large body of work in laboratory animals indicates that ketamine can block the development of opioid tolerance and opioid-induced hyperalgesia and reverse both phenomena, at least partly, when already present. Ketamine has specifically been noted to reduce opioid-induced exacerbations of incisional pain in animals.[13] Curiously, however, studies are mixed as to whether *N*-methyl-D-aspartate receptors strongly support sensitization after incision.[14–16] More broadly, the *N*-methyl-D-aspartate receptor is one of the best studied regulators of pain signaling; these receptors are expressed in various areas in the peripheral and central nervous systems controlling pain sensitization and neural plasticity in many acute and chronic pain states including inflammation, nerve injury, and cancer.

◆ This Editorial View accompanies the following article: Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML: Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. ANESTHESIOLOGY 2010; 113:639–46.

Accepted for publication May 19, 2010. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Many studies have examined ketamine as an adjunctive analgesic in the perioperative period. A recent metaanalysis of 37 trials in more than 2,200 patients indicated that ketamine likely reduces postoperative opioid requirements, at least during the first 24 h.[17] Several studies also reported nominally better pain control, although these observations were not borne out in the combined analysis. The use of ketamine was safe and accompanied by mild side effects, if any. The results of Loftus *et al.*[1] (~30% reduction in morphine consumption over the first 48 h and ~25% reduction in visual analog scale pain score in the postoperative care unit) are similar in magnitude to those previously reported in opioid-naive patients. No attempt has been made to compare directly responses in opioid-naïve patients *versus* those receiving long-term opioid therapy, leaving unresolved the question of whether ketamine is particularly efficacious in the latter group.

Although the results reported by Loftus *et al.*[1] provide reassurance that the adjuvant analgesic effects of ketamine persevere in the perioperative period in patients receiving long-term opioid therapy, many questions remain. First, the dose and infusion duration of ketamine in this study were similar to those used by others for opioid-naive patients, but the infusion stopped at the end of surgery. Perhaps enhanced pain control would have been observed if the infusions were continued on the hospital wards. Second, laboratory studies provide the basis to suggest that persons exposed to higher doses of opioids might receive greater benefit from ketamine, a notion supported by an exploratory *post hoc* analysis undertaken by Loftus *et al.*[1] Whether ketamine is of particular benefit for patients receiving high doses of opioids certainly merits future study. Third, comparing particular benefits and potential disadvantages of various adjunct analgesics head-to-head, including ketamine, α-2-adrenrgic agonists such as dexmedetomidine, and perhaps gabapentin, would be useful for selecting optimal treatment strategies for this group of patients. Finally, we might wonder whether a reduction in opioid requirements translates into any safety or longer term benefits. Perhaps more aggressive postoperative opioid use is as efficacious and safe as introducing a second medication with its inherent risks and benefits. However, if the use of ketamine widens the therapeutic index for opioids or provides longer term benefits, such as a reduced incidence or severity of more prolonged postsurgical pain states, enthusiasm for ketamine might be higher. Indeed some evidence for reduced chronic (6 week) postoperative pain in the ketamine group was found in the present publication; future studies will be needed to determine whether these effects are sustained.

Loftus *et al.*[1] have provided a valuable first effort in addressing a problem of growing importance. Many of us who have embraced the perioperative use of ketamine for patients receiving long-term opioid therapy may be comforted now that there are some actual data supporting such use. Refining our understanding of ketamine's particular value as an adjunct therapeutic in populations vulnerable to suboptimal pain control will be necessary and will allow us to target its use toward those patients who would truly benefit.

Martin S. Angst, M.D., J. David Clark, M.D., Ph.D., Department of Anesthesiology, Stanford University School of Medicine, Stanford, California. djclark@stanford.edu

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Anesthesiology 2010; 113:639–46

Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

Randy W. Loftus, M.D.,* Mark P. Yeager, M.D.,† Jeffrey A. Clark, M.D.,* Jeremiah R. Brown, M.S., Ph.D.,‡ William A. Abdu, M.S., M.D.,§ Dilip K. Sengupta, M.D., Ph.D.,‖ Michael L. Beach, M.D., Ph.D.†

ABSTRACT

Background: Ketamine is an *N*-methyl-D-aspartate receptor antagonist that has been shown to be useful in the reduction of acute postoperative pain and analgesic consumption in a variety of surgical interventions with variable routes of administration. Little is known regarding its efficacy in opiate-dependent patients with a history of chronic pain. We hypothesized that ketamine would reduce postoperative opiate consumption in this patient population.

Methods: This was a randomized, prospective, double-blinded, and placebo-controlled trial involving opiate-dependent patients undergoing major lumbar spine surgery. Fifty-two patients in the treatment group were administered 0.5 mg/kg intravenous ketamine on induction of anesthesia, and a continuous infusion at 10 $\mu g\,kg^{-1}min^{-1}$ was begun on induction and terminated at wound closure. Fifty patients in the placebo group received saline of equivalent volume. Patients were observed for 48 h postoperatively and followed up at 6 weeks. The primary outcome was 48-h morphine consumption.

Results: Total morphine consumption (morphine equivalents) was significantly reduced in the treatment group 48 h after the procedure. It was also reduced at 24 h and at 6 weeks. The average reported pain intensity was significantly reduced in the postanesthesia care unit and at 6 weeks. The groups had no differences in known ketamine- or opiate-related side effects.

Conclusions: Intraoperative ketamine reduces opiate consumption in the 48-h postoperative period in opiate-dependent patients with chronic pain. Ketamine may also reduce opioid consumption and pain intensity throughout the postoperative period in this patient population. This benefit is without an increase in side effects.

What We Already Know about This Topic

- Acute pain management of patients with chronic pain who are opioid-tolerant is often difficult.
- Few interventions have reduced postoperative opioid requirements or pain scores in this patient population.

What This Article Tells Us That Is New

- In a randomized controlled trial, intraoperative administration of ketamine reduced opioid consumption after spine surgery in these patients with chronic pain who are opioid-tolerant.

KETAMINE is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been shown to be useful in the reduction of acute postoperative pain and analgesic consumption in a variety of surgical interventions with variable routes of administration.[1] It has multiple mechanisms of action, including but not limited to decreasing central excitability, decreasing acute postoperative opiate tolerance, and a possible modulation of opiate receptors. Furthermore, it has been shown to be effective in the

* Assistant Professor, † Professor, Department of Anesthesiology, § Professor, ‖ Assistant Professor, Department of Orthopaedic Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire. ‡ Instructor, The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Section of Cardiology, Dartmouth-Hitchcock Medical Center.

Received from the Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire. Submitted for publication January 12, 2010. Accepted for publication April 15, 2010. Support was provided solely from institutional and/or departmental sources. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 13, 2007. Presented at the 57th Annual Meeting of the Association of University Anesthesiologists, Denver, Colorado, April 8, 2010.

Address correspondence to Dr. Loftus: Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr, Lebanon, New Hampshire 03756. randy.loftus@hitchcock.org.

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View: Please see: Angst MS, Clark JD: Ketamine for managing perioperative pain in opioid-dependent patients with chronic pain: A unique indication? ANESTHESIOLOGY 2010;113:514–5.

presence and absence of opiates, nonsteroidal antiinflammatory medications, and acetaminophen.[2,3]

Intraoperative use of preventative ketamine has been shown to generate a modest reduction in acute postoperative opioid consumption (median 33%) and pain intensity (20–25%) up to 48 h after the surgical insult.[4,5] The clinical benefit, however, remains unclear, because (1) opiate-naive patients were largely enrolled; (2) patients typically consumed small amounts of opioid medications and were reasonably comfortable in the postoperative period, making it difficult to assess the impact of the reduction in analgesic consumption on opiate-related side effects; and (3) the side-effect profile of low-dose ketamine was not well characterized. Thus, the last 15 yr has yielded little insight into the utility of preventative NMDA receptor antagonism in patients with a history of chronic pain who use opiate medications preoperatively. This has been suggested as a primary target for research, because patients with chronic pain are thought to be at increased risk of suboptimal postoperative pain management and consequently at increased risk of cardiopulmonary complications and chronic postsurgical pain.[6–9] The primary hypothesis of the current study was that intraoperative preventative ketamine would reduce acute postoperative analgesic requirements in opiate-dependent patients with a history of chronic back pain who are undergoing painful surgery.

Materials and Methods

General Description

This was a randomized, prospective, double-blinded, and placebo-controlled trial investigating the efficacy of preventative ketamine infusions in patients with chronic pain who were undergoing elective back surgery. The study was conducted over a 2-yr period (February 2007 to April 2009) at Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire). Approval was obtained from the Committee for Protection of Human Subjects. Informed patient consent was obtained from all patients.

Adult patients with a history of daily opiate use for at least 6 weeks and chronic back pain for at least 3 months who were scheduled to undergo elective lumbar back surgery requiring in-patient admission to the hospital were considered eligible for enrollment if none of the following exclusion criteria were met: intolerance or known allergy to ketamine, increased intraocular pressure, uncontrolled hypertension, increased intracranial pressure, a history of psychosis, or pregnancy.

Patient Recruitment

The clinical schedules of participating surgeons were reviewed electronically on a daily basis for patients meeting inclusion criteria. Surgeons were notified in advance of patient eligibility so that they could conduct a preoperative discussion of the randomized clinical trial. On the day of surgery, the principal investigator and/or coinvestigators reviewed the study with the patients in the preoperative holding area and obtained informed consent. Duration of daily opiate consumption was confirmed, and in accordance with clinical practice, baseline morphine equivalents were determined based on the preceding 24-h opiate requirements per patient report. The opiate class was tracked and recorded, and standard opiate conversions were used.[10] Patients taking only tramadol were not considered eligible for enrollment. Patients taking tramadol in addition to other opiate medications were included, but use of tramadol was tracked and recorded as an adjunctive agent for later comparisons. Patients were also identified by the primary anesthesia team, received a standard preoperative evaluation, and provided consent for general anesthesia.

Study Protocol

After consent, a computer-generated block randomization scheme was used to randomize patients in groups of eight to one of two treatment regimens: racemic ketamine (JHP Pharmaceuticals, Parsippany, NJ) or placebo (saline). Principal investigators, patients, nursing staff, and anesthesia providers were blinded to the treatment assignments during the entire hospital stay, through the first surgical follow-up visit, and during data analysis. All participants were asked to use a visual analog scale to rate their average daily pain preoperatively, postoperatively, and at the first follow-up visit.

A standardized anesthesia induction and maintenance protocol was followed. This protocol included 2 mg midazolam before leaving the preoperative holding area, 2–3 μg/kg fentanyl before induction, 2–2.5 mg/kg propofol on induction, and isoflurane for maintenance of anesthesia. Unless contraindicated (fusion procedure), all anesthesia providers were asked to administer 15 mg ketorolac to patients before emergence. Nitrous oxide was not allowed because of its NMDA antagonistic properties. All additional adjunctive agents administered intraoperatively were tracked and recorded.

Patients were allowed to receive morphine while anesthetized up to their daily opiate dose, plus an additional 0.1 mg/kg morphine at or before emergence. Additional opiates could be used by the anesthesia team if clinically indicated. All patients were to have patient-controlled analgesia for initial postoperative pain control. Patient-controlled analgesia management was directed by the primary surgical service according to standard practice at Dartmouth-Hitchcock Medical Center. Typical management involved transition from the patient-controlled analgesia (morphine, fentanyl, or hydromorphone) to medications by mouth as needed on postoperative day 1 (after 24 h).

The study infusions were prepared by the investigational pharmacy preoperatively and labeled as study drug/placebo. Intraoperatively, the solutions were connected to preprogrammed infusion pumps so that the anesthesia provider would simply need to connect the pumps to the patients intravenously and run as programmed. All patients received 0.5 mg/kg of the study solution (assuming in all cases that the solution was ketamine at 10 mg/ml) on induction and an

infusion of 10 μg kg^{-1}min^{-1} started before incision and terminated on closure of the incision. In addition, all anesthesia providers were asked to provide 8 mg of dexamethasone (Decadron®) on induction.

Intraoperative maximal and minimal heart rate and blood pressure were recorded by the anesthesia providers on the standard anesthetic record, and postoperative opioid requirements were followed for 48 h by the principal investigator(s). The incidence of opioid-related side effects (nausea, vomiting, urinary retention, hypoactive bowel sounds), number of house officer interventions, length of postanesthesia care unit (PACU) stay and hospital stay, and ketamine-related side effects during the perioperative period were systematically evaluated and recorded.

Basic demographic information [American Society of Anesthesiology Health Classification Status, SF-36 scores, age, sex, morphine opiate equivalents (milligrams per hour intravenous), baseline average daily pain intensity as rated on visual analog scales, baseline heart rate and blood pressure, opiate medication class (type), use of adjunctive medications (nonsteroidal agents, acetaminophen, synthetic opiates, lidocaine [Lidoderm® patches], antidepressants, anticonvulsants, muscle relaxants, and anxiolytics), use of β-adrenergic receptor blockers and additional antihypertensive agents, functional status, history of prior back surgery, surgeon, surgical duration, estimated blood loss, and procedure type (number of levels, with or without instrumentation) were obtained and recorded. In addition, opiate and adjunctive medication type used in the intraoperative, postoperative, and 6-week follow-up visit were also tracked and recorded.

A follow-up visit coordinated with the first postoperative surgical visit was conducted by a research nurse to evaluate opioid use, use of adjunctive agents, use of conservative measures (physical therapy), and associated side effects through use of a standard survey. The functional status of patients was also reviewed at this time.

Statistical and Power Analysis

Power. We conducted a retrospective chart review of 20 opiate-dependent patients with chronic pain who underwent back surgery at Dartmouth-Hitchcock Medical Center in the 6-month period preceding protocol submission to the Committee for Protection of Human Subjects. Recorded information included mean values and SD for total opiate requirements at 48 h. Using the information obtained from this review (mean $\pm$ SD 48-h opiate consumption, 500 $\pm$ 300 mg by mouth) and an estimated treatment effect of a 40% reduction in postoperative analgesic requirements,[4,5] two-tailed hypothesis testing resulted in the conclusion that we would need 48 participants per group (96 total participants) to achieve a power of 0.9 to detect a 40% treatment effect with favorable type I error rates.

Statistical Analysis. The primary outcome was total morphine consumption (in terms of intravenous morphine equivalents) during the first 48 h after the procedure. Secondary outcomes included visual analog scores during the first 48 h and at 6 weeks, 6-week morphine equivalents, hemodynamic changes from baseline in the intraoperative and 48-h postoperative periods, duration of PACU and hospital stay, and differences in adjunctive and conservative measures at 6 weeks compared with preoperative patient reports. The primary comparison was an unadjusted analysis using an unpaired Student *t* test. Categorical binary outcomes were compared using Fisher exact test. A multivariate regression approach was then undertaken to assess the impact of potentially confounding covariates. We transformed 24- and 48-h morphine consumption on the log scale to achieve normality and equal variance, because the distribution of preoperative morphine consumption was not normal. We applied standard graphical and computational diagnostics to determine adequacy of model fit. Binary variables were modeled in a similar fashion using generalized linear models with a logistic link and correction for overdispersion. These variables were reported in their original metric for descriptive purposes. Dependent variables, such as the number of side effects, were treated using ordinal generalized linear models. We considered missing as missing at random. Results were presented using 95% confidence intervals. A *P* value of less than 0.05 was taken to indicate statistical significance. No correction was made for multiple comparisons, because comparisons other than the primary outcome were considered exploratory. Our group has had extensive experience using STATA software (Stata Corporation, College Station, TX) for data analysis. This package was sufficient for all the analyses described above.

Results

Three hundred and one patients with chronic back pain scheduled for elective lumbar surgery requiring hospital admission were screened over a 2-yr period. Of these patients, 165 (55%) were eligible for enrollment. Of 165 eligible patients, 101 (61%) were randomized to one of the two treatment groups. There were no significant differences in terms of age, sex, and number of surgical spine levels in those patients enrolled and those that declined (data not shown). Less than 10% of the data pertaining to the primary outcome (morphine consumption during the first 48 h) was missing in the final analysis. Missing data were due to unanticipated early patient discharge with equal numbers in both treatment groups. No patients enrolled in the study were excluded from the primary analysis.

As shown in table 1, patients in both the treatment and placebo group were comparable preoperatively. Patients reported similar pain, daily opiate use, and conveyed a similar degree of mental health, as reflected in the mental component score.

Patients in the treatment and control groups were also comparable in the operating room (table 2), PACU (table 2), and hospital ward (table 3) environments. Significant differences between groups included only that (1) patients in the treatment group required 24% less intraoperative opiate

Table 1. Preoperative Demographics

	Placebo	Ketamine	*P* Value
Patients, No.	50	52	—
Age, yr	51.4 ± 14.4	51.7 ± 14.2	0.92
Weight, kg	89.3 ± 23.8	95.4 ± 17.7	0.15
BMI, kg/m^2	30.7 ± 6.7	32.5 ± 6.7	0.20
Female, %	44.0	36.5	0.44
ASA Status			
I–II	70.0	69.2	0.93
III–IV	30.0	30.8	—
Preoperative Medications			
Synthetic Opioid	4.0	0.0	0.23
Acetaminophen or Nonsteroidal Drug	76.0	88.5	0.09
Muscle Relaxant	8.0	11.5	0.39
Anticonvulsant	32.0	26.9	0.57
Antidepressant	40.0	32.7	0.44
Lidoderm Patch	8.0	7.7	0.62
Antihypertension Other	38.0	36.5	0.87
β-Adrenergic Receptor Blocker	20.0	23.1	0.70
Prior Back Surgery	34.0	36.5	0.78
MCS, %	42.7 ± 14	44.8 ± 14	0.49
VAS, cm	6.9 ± 1.6	7.0 ± 1.8	0.840
Duration of Chronic Pain, months	95 ± 108	70 ± 73	0.166
Functional Capacity (Working), disabled, working	1.9 ± 0.7	1.9 ± 0.8	0.865
Morphine Equivalents, median (interquartile range)	0.5 (03–1.2)	0.4 (0.3–0.9)	0.552
Heart Rate, beats/min	77 ± 13	73 ± 14	0.188
Systolic Blood Pressure, mmHg	135 ± 20	131 ± 15	0.248
Diastolic Blood Pressure, mmHg	82 ± 13	78 ± 11	0.094

Data are presented as mean ± SD or as a percentage. Mental component summary (MCS) is a validated measure of mental health that takes into account correlation among the eight short-form-36 scales. The general population mean is 50 with an SD of 1036.[35]

ASA = American Society of Anesthesiologists; BMI = body mass index; VAS = visual analog scale.

Table 2. Operative and PACU Characteristics

	Placebo	Ketamine	*P* Value
Surgeon, %			
1	66.0	69.4	0.719
2	34.0	30.6	—
Instrumented Fusion, %	58.0	58.0	1.000
Inhalational Agent, %*			
1	98.0	96.2	1.000
2	2.0	1.9	—
3	0.0	1.9	—
Adjunctive Agent, %†	6.0	26.0	0.006
Levels, no.	1.6 ± 0.9	2.0 ± 0.9	0.021
Duration of Surgery, min	211 ± 78	210 ± 94	0.954
Blood Loss, ml	642 ± 602	650 ± 765	0.956
Morphine Equivalents, mg	67 ± 44	51 ± 27	0.034
Fentanyl, total μg	515 ± 347	452 ± 243	0.289
Morphine, total mg	11 ± 21	5 ± 7	0.071
Dilaudid, mg	0.4 ± 1.6	0.1 ± 0.6	0.188
Dexamethasone, mg	6.4 ± 3.0	6.2 ± 3.3	0.837
Midazolam, mg	2.3 ± 1.0	2.2 ± 1.0	0.656
Propofol, mg	220 ± 65	210 ± 55	0.403
PACU Adjunctive Agents†	18.4	26.0	0.361

* Inhalational agent 1 = isoflurane, 2 = sevoflurane, 3 = desflurane.
† Nonsteroidal, nalbuphine hydrochloride, dexamethasone, acetaminophen, and/or ketorolac tromethamine.
PACU = postanesthesia care unit.

medications (67 ± 44 mg, placebo; 51 ± 27 mg, treatment) and (2) patients in the treatment group received nonsteroidal adjunctive medications intraoperatively more frequently (6.0%, placebo; 26%, treatment; $P = 0.006$).

As shown in table 4, patients in the treatment group consumed 37% less morphine on average during the 48-h postoperative period (309 ± 341 mg, placebo; 195 ± 111 mg, treatment; $P = 0.029$) and 30% less morphine on average during the 24-h postoperative period (202 ± 176 mg, placebo; 142 ± 82 mg, treatment; $P = 0.032$). A subgroup analysis of only those patients who did not receive nonsteroidal medications intraoperatively revealed similar results in terms of the primary outcome of 48-h morphine consumption (323 ± 347 mg, placebo; 203 ± 109 mg, treatment; 37% reduction; $P = 0.045$). Patients in the treatment group also reported a 26.7% reduction in pain intensity in the PACU (5.6 ± 3.0 cm, placebo; 4.1 ± 3.1 cm, treatment; $P = 0.033$) and a 26.2% reduction in pain intensity at their first follow-up visit at 6 weeks (4.2 ± 2.4 cm, placebo; 3.1 ± 2.4 cm, treatment; $P = 0.026$). There was no difference between groups in reported pain intensity (visual analog

Table 3. Hospital Ward

	Placebo	Ketamine	*P* Value
Tylenol or Nonsteroidal Drug, %	86.0	94.2	0.144
Antidepressant, %	40.8	34.6	0.520
Anxiolytic, %	32.7	25.0	0.396
Anticonvulsant, %	38.8	30.8	0.398
Muscle relaxant, %	14.3	21.2	0.367
Synthetic opioid, %	4.1	0.0	0.233
Dexamethasone, mg	4.1	11.5	0.155

Table 4. Outcomes

	Placebo	Ketamine	*P* Value
24 hr ME, total mg/24 hr	202 (176)	142 (82)	0.032
48 hr ME, total mg/48 hr	309 (341)	195 (111)	0.029
48 hr ME Adjusted, mg*	323 (347)	203 (109)	0.045
PACU VAS, cm	5.6 (3.0)	4.1 (3.1)	0.033
PACU ME, mg total	22 (20)	18 (14)	0.218
Ward VAS 24-hr, cm	4.8 (2.4)	4.7 (2.7)	0.902
Ward VAS 48-hr, cm	5.3 (2.2)	5.4 (2.1)	0.838
6-wk ME, mg/hr intravenous morphine	2.8 (6.9)	0.8 (1.1)	0.041
6-wk VAS, cm	4.2 (2.4)	3.1 (2.4)	0.026
PACU Discharge Time, min	160 (77)	174 (62)	0.321
Hospital Discharge Time, min	4,571 (4,099)	4,364 (2,296)	0.728

Data are presented as mean (SD).

* Analysis of patients who did not receive intraoperative nonsteroidal medications (ketorolac).

ME = morphine equivalent; PACU = postanesthesia care unit; VAS = visual analog scale.

scores) during the 48-h postoperative period. The reduction in pain intensity at 6 weeks in the treatment group occurred despite a 71% reduction in opiate consumption in the treatment group compared with placebo (2.8 ± 6.9 mg/h intravenously, placebo; 0.8 ± 1.1 mg/h intravenously, treatment; $P = 0.041$). There were no differences between groups in terms of duration of PACU or hospital stay.

There were no significant differences between groups in terms of ketamine or opiate-related side-effects in the acute postoperative period or at the first postsurgical visit (table 5). Ketamine was not associated with a significant change in heart rate or blood pressure from baseline values during the intraoperative, PACU, or hospital ward periods (data not shown). The timing of the first postoperative visit was no different between groups and averaged roughly 6 weeks, and there was no difference between groups in terms of use of physical therapy (data not shown). An unexpected finding was that all adjunctive medications used by patients at 6 weeks were similar in both groups (data not shown) except that patients in the treatment group used antidepressant agents more infrequently than patients in the placebo group (10.6%, placebo; 0%, treatment; $P = 0.023$).

An exploratory analysis was completed to evaluate the impact of ketamine stratified according to preoperative morphine use. Intraoperative ketamine reduced 48-h morphine consumption by 52% in patients with morphine equivalents of greater than 0.5 mg/h intravenous (471.3 ± 441.3 mg placebo; 241.3 ± 145.7 mg ketamine; $P = 0.031$) placebo, whereas it had no effect in patients consuming less than 0.5 mg/h intravenously preoperatively (166.3 ± 86.8 mg placebo; 172.7 ± 83.2 mg ketamine). A similar effect was seen at 24 h (table 6).

A multivariate linear regression model was used to predict 48-h morphine use. We included preoperative morphine and 48 h morphine consumption using a log scale to account for skewed nature of preoperative morphine use. We also included age, American Society of Anesthesiology Health Classification status greater than II, sex, and the use of nonsteroidal antiinflammatory medications (binary) either preoperatively or in the postoperative period. Residual plots did not demonstrate lack of fit. There was no difference in the estimated effect of ketamine with the covariate-adjusted model.

Discussion

We have demonstrated that intraoperative preventative ketamine reduces opiate consumption in the acute postoperative period by 37% in opiate-dependent patients with chronic pain who are undergoing painful back surgery. In addition, it seems to reduce pain intensity postoperatively in the PACU and at 6 weeks and to reduce consumption of morphine at the first postoperative visit. The findings of this study add considerably to the body of literature pertaining to the efficacy of ketamine in preventative NMDA receptor antagonism.

Intraoperative preemptive and preventative use of low-dose racemic ketamine has been shown to reduce acute postoperative analgesic consumption and pain intensity in opiate-naive

Table 5. Adverse Events

	Placebo	Ketamine	*P* Value	RR (95% CI)
48 hr				
Nausea	22.5	26.9	0.603	1.20 (0.60, 2.38)
Vomiting	12.2	15.4	0.648	1.26 (0.47, 3.36)
Hallucinations	2.0	1.9	0.737	0.94 (0.06, 14.65)
Urinary Retention	2.0	7.7	0.200	3.77 (0.44, 32.56)
6 wk				
Nausea	17.0	11.8	0.458	0.69 (0.26, 1.84)
Vomiting	8.5	9.8	0.552	1.15 (0.33, 4.04)
Hallucinations	23.4	11.8	0.128	0.50 (0.20, 1.25)
Constipation	57.5	45.1	0.222	0.79 (0.53, 1.16)

CI = confidence interval; RR = risk ratio.

Table 6. Ketamine Effect Stratified According to Preoperative Morphine Use

	Treatment			Placebo			
	N	Mean (mg)	SD	N	Mean (mg)	SD	*P* Value
≥0.556 mg/hr intravenously							
24-hr ME	17	168.8	94.4	22	302.5	216.8	0.014
48-hr ME	16	241.3	145.7	22	471.3	441.3	0.031
<0.556 mg/hr intravenously							
24-hr ME	34	129.3	73.8	27	119.9	59	0.58
48-hr ME	33	172.7	83.2	25	166.3	86.8	0.78

ME = morphine equivalent.

patients undergoing a variety of surgical procedures associated with mild to moderate postoperative pain.[4–5,11–14] Some evidence also suggests that this effect is maintained for a longer period of time.[15] Although these findings have been extrapolated to opiate-dependent patients with chronic pain, the clinical utility and side-effect profile of intraoperative ketamine in such patients is, until now, entirely unknown.[16] Further, because prior studies included opiate-naive patients, opiate consumption in the postoperative period was moderate (less than 40 mg); thus, the reduction in opiate consumption generated by ketamine was small (median reduction, 12.8 mg).[4,5] As a result, the proven clinical benefit of ketamine in terms of reduction in opiate-related side-effects has been minimal. Finally, the impact of ketamine on opiate tolerance or hyperalgesia has not been well described.[17,18]

The purpose of this study was to determine the efficacy of intraoperative preventative ketamine in opiate-dependent patients with chronic pain. This information is especially valuable because many factors related to chronic pain, such as underlying psychiatric disorders (depression and anxiety), opioid tolerance, and opioid-induced hyperalgesia, make management of acute on chronic postoperative pain difficult to assess and often suboptimal.[19–21] Even without a history of chronic pain and/or opiate dependence, evidence suggests that postoperative pain continues to be undermanaged.[22,23] It is well known that poorly controlled acute postoperative pain is associated with cardiopulmonary complications and an increased risk of development of chronic postsurgical pain.[24,25] Thus, multimodal therapy, including both nonopioid adjunctive medications (ketamine, nonsteroidal antiinflammatory agents, acetaminophen, and anticonvulsants) and opioids is often required in this patient population to minimize potential complications related to suboptimal pain management.[26] As such, it is important that we better understand the clinical utility of these agents so that we may be able to maximize our efforts to improve patient safety, outcomes, and overall satisfaction.

The minimum daily dose of opioid medication that will induce an increased risk of opioid-induced hyperalgesia or tolerance is not known, but it is generally believed that even moderate daily opioid consumption (less than 40 mg by mouth daily) is enough.[16] The average daily opioid use of patients in this study was substantially greater and similar in both groups and falls within the previously reported range for opiate-dependent patients.[6] The exact number of opiate-dependent patients presenting for surgery is unknown, but the use of opioids for management of outpatient malignant and nonmalignant pain is increasing, second only to nonsteroidal medications. In fact, 44% of all patients receiving any analgesic agent will be prescribed opioids.[16,27] Thus, the results of this study may be applicable to a large patient population.

We have demonstrated that preventative ketamine use in opiate-dependent patients with chronic pain reduces total opiate consumption in the postoperative period up to 48 h after surgery. The opiate-sparing effect of ketamine demonstrated in this study is consistent with prior reports in opiate-naive patients but is of greater magnitude (114 *vs.* 40 mg), allowing a true assessment of the clinical impact of ketamine in terms of reduction in opiate-related side-effects.[4,5] An interesting finding is that there was much less variation in 24- and 48-h morphine consumption in patients treated with ketamine compared with placebo. In addition, the opiate-sparing effect of ketamine was greatest during the 24–48-h postoperative period as opposed to the first 24 h, as previously reported. Further, an exploratory analysis suggests that ketamine may be most efficacious in patients with chronic pain who consume at least 0.556 mg/h morphine intravenously (at least 40 mg by mouth daily). These findings suggest that (1) not all opiate-dependent patients with chronic pain require adjunctive medication such as ketamine, but there is a patient subset that does very poorly without adjunctive therapy that needs to be identified preoperatively; and (2) the molecular mechanism of action of ketamine at the transcriptional and translational level in opiate-dependent patients with chronic pain may be different from that in opiate-naive patients. This requires further study. Patients in the treatment group also required less intraoperative opiate and reported less pain in the PACU, with the reduction in pain intensity significantly greater than previously reported. This may be related to residual sedation and analgesia from ketamine, but when considering the magnitude of the effect, it is most likely a combination of ketamine-related analgesia and diminished hyperalgesia. This premise is supported by prior studies demonstrating an association between increased intraoperative opioid use and more difficult postoperative pain management secondary to opioid-induced hyperalgesia.[28,29] Finally, because patients in the treatment group

achieved a similar degree of pain control with significantly less opioid administration, this may argue for a reduction in opiate tolerance as an additional mechanism of action.[16]

We have also shown that ketamine reduced pain intensity and analgesic consumption up to 6 weeks in the postoperative period. This time period of follow-up was chosen because postsurgical pain typically resolves by 4 weeks.[16] As such, a reduction in pain intensity at 6 weeks would represent a potential reduction in chronic postsurgical pain, an outcome of interest to primary care physicians, surgeons, and, increasingly, to anesthesiologists.[30]

We believe that the reduction in pain intensity at 6 weeks was most likely due to a combination of reduced central sensitization through NMDA receptor antagonism and improved pain control in the acute postoperative period (PACU). However, the mechanism may be more complex, because patients in the treatment group reported significantly less antidepressant use at the first postoperative visit compared with placebo, and there was no significant difference between groups preoperatively. This finding is not entirely surprising, because intravenous ketamine has been shown to acutely improve symptoms of major depressive disorder, probably as a result of inhibition of both serotonin and norepinephrine reuptake.[31] Although preliminary, this finding requires further evaluation.

The combination of these findings suggests that the efficacy of ketamine in this patient subset is due to a complex mechanism of action, involving not only NMDA and opiate receptors but also the balance between excitatory and inhibitory neurotransmitters. As such, these findings could potentially be extrapolated to the chronic pain patient population. With multiple sites of action and receptor subtypes as supported by this study, one can hypothesize that ketamine might prove to be efficacious as a multimodal therapy in a number of chronic pain states. In fact, some evidence suggests that it is useful in central pain, complex regional pain syndrome, fibromyalgia, ischemic pain, orofacial pain, and acute on chronic neuropathic pain. However, the current evidence consists mostly of small, uncontrolled studies and/or case reports.[18] This is the largest controlled, randomized study confirming both short- and long-term benefits of preventative ketamine use in patients with acute on chronic mixed nociceptive and neuropathic pain. Based on the findings of this study, the next logical step is systematically evaluating the impact of ketamine in patients with chronic, mixed neuropathic, and nociceptive pain who are not undergoing surgery. This would require hospital admission.

Treatment groups were largely comparable preoperatively, intraoperatively, and postoperatively both in the PACU and on the hospital ward. Nonsteroidal and acetaminophen medications were combined in the analysis because prior studies have documented similar efficacy in reduction in postoperative pain and opiate sparing.[32,33] The only clinically relevant difference between groups was increased intraoperative use of ketorolac in the treatment group. However, a subgroup analysis excluding those patients who received intraoperative ketorolac revealed similar results. Further, the effect of ketamine remained significant despite adjustment for potential confounders such as patient age, sex, preoperative morphine use, and nonsteroidal drug use (preoperative and postoperative). Although it is unclear to what extent preoperative morphine use increases postoperative opiate consumption,[30] and there was no significant difference in morphine use between groups preoperatively, we still thought it prudent to ensure that the effect of ketamine remained despite adjustments for this potential confounder given the complexity of the patient population selected for study. We also adjusted for patient age and sex given a recent report that these, in addition to preexisting pain and anxiety, are important predictors for difficult postoperative pain management in the general operative patient population.[34] However, predictors for postoperative pain and morphine consumption in opiate-dependent patients with chronic pain are not yet known.

All analyses beyond the primary outcome (48 h postoperative morphine consumption) were secondary and should be interpreted with caution. Further study should be done to assess the relative efficacy of intraoperative, racemic ketamine in patients with varying degrees of preoperative pain, anxiety, depression, morphine consumption and in patients with different subsets of chronic pain (neuropathic *vs.* somatic).

In conclusion, we have rigorously tested the efficacy of ketamine in opiate-dependent patients with chronic back pain undergoing painful surgery. The findings of this study confirm that intraoperative use of preventative ketamine reduces postoperative opiate consumption in this patient population. The results also suggest that its use is beneficial for these patients in terms of reducing both acute postoperative and postsurgical chronic pain. Further, ketamine may be most efficacious in patients who consume higher amounts of preoperative opiate medications. The benefit of intraoperative ketamine is without an apparent increase in side effects and is likely due to a combination of a reduction in central sensitization *via* NMDA receptor antagonism, reduction in opiate tolerance, and some impact on the balance of neurotransmitters. For these reasons, low-dose ketamine should be considered as part of multimodal therapy for all patients with chronic pain who are undergoing painful surgery.

The authors thank Michelle C. Parra, M.D., Assistant Professor, Department of Anesthesiology, and Derrith Guadagni, R.N., and Dawne Mortenson, R.N., B.S.N., Department of Orthopaedic Surgery, and the Investigational Pharmacy, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

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