

Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use

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Abstract

The aim of the study was to evaluate post-operative pain and analgesic use after pre-operative or post-incisional i.v. fentanyl plus low dose i.v. ketamine vs. a standard treatment receiving i.v. fentanyl but not ketamine. Men undergoing radical prostatectomy under general anesthesia were randomly assigned in a double-blinded manner to one of three groups. Patients received i.v. fentanyl before incision followed by an i.v. bolus dose (0.2 ml kg⁻¹) and an i.v. infusion (0.0025 ml kg⁻¹ min⁻¹) of 1 mg ml⁻¹ ketamine (group 1) or normal saline (groups 2 and 3). Seventy minutes after incision, patients received i.v. fentanyl followed by an i.v. bolus dose (0.2 ml kg⁻¹) and an i.v. infusion (0.0025 ml kg⁻¹ min⁻¹) of saline (groups 1 and 3) or ketamine (group 2). Pain, von Frey pain thresholds, and cumulative morphine consumption using patient-controlled analgesia (PCA) were assessed up to 72 h after surgery. 143 patients completed the study (group 1, $n = 47$; group 2, $n = 50$; group 3, $n = 46$). Cumulative PCA morphine (mean \pm SD) did not differ significantly among groups (group 1, 92.3 ± 45.9 mg; group 2, 107.2 ± 58.4 mg; group 3, 103.6 ± 50.4 mg; $P = 0.08$ for groups 1 vs. 2, and groups 1 vs. 3). On day 3, the hourly rate (mean \pm SEM) of morphine consumption was significantly lower ($P < 0.0009$) in group 1 (0.61 ± 0.013 mg h⁻¹) than group 2 (0.86 ± 0.011 mg h⁻¹) and group 3 (0.89 ± 0.008 mg h⁻¹). Pain scores and von Frey pain thresholds did not differ significantly among groups. Two-week and 6-month follow-ups did not reveal significant group differences in pain incidence, intensity, disability or mental health. Pre-operative, low-dose administration of i.v. ketamine did not result in a clinically meaningful reduction in pain or morphine consumption when compared with post-incisional administration of ketamine or a saline control condition.

Keywords: Analgesia; Fentanyl; Ketamine

1. Introduction

Ketamine hydrochloride operates on multiple receptor systems (Schmid et al., 1999). However, its property as a non-competitive NMDA receptor antagonist generated

a new focus of research activity once this receptor-ion channel complex was found to play a critical role in the induction and maintenance of central sensitization and pathological pain (Wilcox, 1991; Woolf and Thompson, 1991). The mechanism by which pain and analgesic consumption are reduced after pre-emptive administration of local anesthetics and opioids is believed to involve the prevention of NMDA-mediated sensitization of spinal cord dorsal horn neurons (Kissin, 2000; Woolf and Chong, 1993). Thus, the NMDA channel blocker ketamine has been of particular interest in evaluating the hypothesis that ketamine administration before surgery would reduce pain

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and analgesic consumption relative to saline administration or to ketamine administration after incision.

Studies of pre-emptive analgesia using intravenous low-dose ketamine have yielded mixed results (Katz, 2003; McCartney et al., 2004; Schmid et al., 1999). This is in part due to the large inter-study variability in surgical procedure, patient population, dose of ketamine, use of additional analgesic agents intraoperatively and study design. One of the aims of the present study was to evaluate the effects on post-operative pain and morphine consumption of pre-incisional vs. post-incisional i.v. administration of the mu opioid agonist fentanyl plus low-dose ketamine. Use of these two agents together would be expected to capitalize on their combined actions in reducing nociceptive input and central sensitization (Chapman and Dickenson, 1992; Dickenson, 1997). We hypothesized that morphine consumption would be lower in the pre-incisional group compared with the post-incisional group.

Debate about the efficacy of pre-emptive analgesia stems in part from a fundamental misconception about its definition (Katz, 2003; Kissin, 2000). The typical two-group design that compares administration of an agent before vs. after incision or surgery fails to control for the possibility that early and late noxious intraoperative stimuli contribute equally to post-operative central sensitization. Two group studies that do not show a significant difference in outcome leave open the question of whether the absence of an effect reflects the relative efficacy of post-operative blockade or the inefficacy of pre-operative blockade in reducing central sensitization (Katz, 2003; Katz et al., 2003).

Therefore, the second aim of the present study was to evaluate post-operative pain and analgesic use after pre-operative or post-incisional i.v. fentanyl plus low dose i.v. ketamine vs. a standard treatment control condition consisting of i.v. fentanyl but not ketamine. Men undergoing radical prostatectomy under general anesthesia were randomly assigned in a double-blinded manner to one of three groups: (1) i.v. fentanyl plus low dose i.v. ketamine (bolus plus infusion) before incision and i.v. fentanyl plus saline (bolus plus infusion) after incision; (2) i.v. fentanyl plus i.v. saline (bolus plus infusion) before incision and i.v. fentanyl plus low dose i.v. ketamine (bolus plus infusion) after incision; or (3) i.v. fentanyl plus i.v. saline (bolus plus infusion) before and after incision. We hypothesized that post-operative pain and morphine consumption would be lowest in the pre-incision group and highest in the control group.

2. Materials and methods

Approval to carry out the study was obtained from The Toronto Hospital Research Ethics Board. All patients gave their written informed consent to participate before entering the study.

Patients scheduled for radical prostatectomy for prostate cancer were eligible for recruitment into the study. Inclusion criteria were American Society of Anesthesiologists physical status I–II, age between 19 and 75 years and able to speak and read English. Exclusion criteria were contraindications to (iv) patient-controlled analgesia (PCA) with morphine, American Society of Anesthesiologists physical status >II, history of major psychiatric disorder, and chronic opioid use.

2.1. Randomization and blinding procedures

A randomization schedule was computer-generated (Dallal, 1988) and provided to the hospital pharmacist who prepared and dispensed the study drug. The randomization schedule specified the group (1, 2, or 3) to which each prospective patient would be allocated upon entry into the trial. An opaque envelope containing the patient number and group assignment was prepared, sealed and numbered for each patient by the hospital pharmacist.

All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was also unaware of group allocation.

2.2. Drug preparation

A standard volume of ketamine hydrochloride and normal saline was prepared in two separate 60 ml syringes, coded for blinding purposes, and dispensed by the hospital pharmacy on the day of surgery. The syringes were labeled 'pre-incision' and 'post-incision'. For group 1 and 2 patients, one syringe contained 60 ml ketamine hydrochloride (1 mg ml^{-1}); the second contained 60 ml normal saline. For group 3 patients, both syringes contained 60 ml normal saline. The pharmacist who dispensed the study medications was not involved in any other aspect of the study.

2.3. Pain assessment instruments

2.3.1. Visual analogue scale (VAS)

The VAS provides a simple, efficient, and minimally intrusive measure of pain intensity that has been used widely in research settings where a quick index of pain is required and to which a numerical value can be assigned (Katz and Melzack, 1999). The VAS consists of a 10 cm horizontal line with the two endpoints labeled 'no pain' and 'worst possible pain', respectively. The patient is required to mark the 10 cm line at a point that corresponds to the level of pain intensity he presently feels. The distance in centimeters from the low end of the VAS and the patient's mark is used as a numerical index of pain intensity. Pain was assessed with patients at rest (VAS-R) and after standard mobilization (VAS-M) by asking patients to roll from a supine to a side-lying position and perform two maximal inspirations before rating their pain.

2.3.2. McGill Pain Questionnaire (MPQ)

The MPQ was developed by Melzack (1975) to obtain quantitative and qualitative measures of the experience of pain. The MPQ yields two global scores, the pain rating index (PRI) and the present pain intensity (PPI), which have been found to provide valid and reliable measures of pain (Katz and Melzack, 1999; Melzack, 1975). The PRI is the sum of the rank values of the words chosen from 20 sets of qualitative words, each set containing 2–6 adjectives that describe the sensory, affective and evaluative properties of pain. The lists of pain descriptors are read to the patients who are asked to choose the word in each category that best describes their pain at the moment. The PPI is rated on a scale of 0–5 as follows: 0, none; 1, mild; 2, discomforting; 3, distressing; 4, horrible; and 5, excruciating.

2.3.3. von Frey filaments

Secondary mechanical hyperalgesia to punctate stimulation applied to the skin was assessed using von Frey filaments (Smith and Nephew Rolyan Inc., Menomonee Falls, WI) that consist of a set of 20 individual nylon filaments of equal length (38 mm) ranging from 0.06 to 1.14 mm in diameter. Each filament has been assigned a value that represents the logarithm of the force (in mg) required to bend it maximally when pressed against the skin. To minimize the assessment burden on the patients, we used every other filament beginning with the smallest (0.06 mm). On each trial, a filament was applied to the designated point on the skin for approximately 1 s. Trials were separated by an interval ranging from 5 to 15 s in order to reduce the likelihood of anticipatory responses. Filaments were applied in ascending serial order. Touch threshold (TT) was defined by the value (force in log mg) associated with the filament that patients first reported a sensation of touch. Pain threshold (PT) was defined by the value (force in log mg) associated with the filament that patients first reported as being uncomfortable or painful. PTs were obtained from two regions of the body: a control site on the inner forearm and a test site approximately 10 cm from the wound dressing.

2.4. Measures of psychosocial functioning

2.4.1. Mental Health Inventory (MHI)

The MHI (Ware et al., 1979) is a self-administered questionnaire that measures symptoms of psychological distress and well-being. The present study used an 18-item version of the MHI that consists of a total score and five subscales: anxiety, depression, loss of behavioral/emotional control, positive affect, and interpersonal ties (Weinstein et al., 1989). Subjects responded to each of the 18 statements on the basis of how often 'in the past month' they have experienced each symptom. Each statement is accompanied by a six choice response set ranging from 1 = all of the time to 6 = none of the time. The total score, which we report in the present study, ranges from 0 to 108

with higher scores indicative of better mental health. The MHI was administered prior to surgery. Internal reliability of the MHI subscales by Cronbach's alpha ranged from 0.10 (loss of behavioral/emotional control) to 0.85 (depression).

2.4.2. Spielberger State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger et al., 1970) is composed of two forms, each of which measures separate dimensions of anxiety. The STAI-S consists of 20 statements and measures 'state anxiety'. The patients are required to respond on the basis of how they are feeling 'right now' (i.e. at the moment when completing the form). The STAI-T measures anxiety as an enduring personality trait and consists of another 20 statements that pertain to how the patients 'generally feel'. The STAI-S has been shown to be sensitive to psychological manipulations that alter anxiety level. Test-retest reliability coefficients of the STAI-T have been reported to be relatively high, reaching approximately 0.70 after a 3-month interval, and increasing with decreasing time between testings. The STAI has also shown relatively high correlations with other well known measures of anxiety. Only the STAI-S was used in the present study. Internal reliability of the STAI-S by Cronbach's alpha was 0.90.

2.4.3. Follow-up Pain Questionnaire (FUPQ)

The FUPQ is a brief inventory designed to assess the presence, intensity, location, frequency, and quality of long-term post-surgical pain. Items also assess pain interference in daily life, methods of pain relief sought, medication use and aggravating and relieving factors. The FUPQ was modeled after similar pain assessment measures including the MPQ (Melzack, 1975) and a follow-up interview form used to assess long-term pain after surgery (Dajczman et al., 1991). The FUPQ was administered at the 6-month post-surgical interview.

2.5. Procedures

2.5.1. Preoperative assessment

A member of the research team approached prospective patients who were informed of the nature of the study, screened for eligibility and recruited if interested. Following informed written consent, patients completed the MHI and STAI-S. Patients were familiarized with the VAS rating scales and were shown a PCA pump and instructed in its use.

2.5.2. Pre-incisional and post-incisional administration of ketamine and saline

On the morning of surgery a research nurse drew up the appropriate volumes (based on the patient's weight) from the two 60 ml coded syringes that had been prepared and dispensed by the pharmacy. The first and second syringes, labeled 'pre-incision' and 'post-incision', respectively, contained ketamine (1 mg ml⁻¹) and saline for group 1,

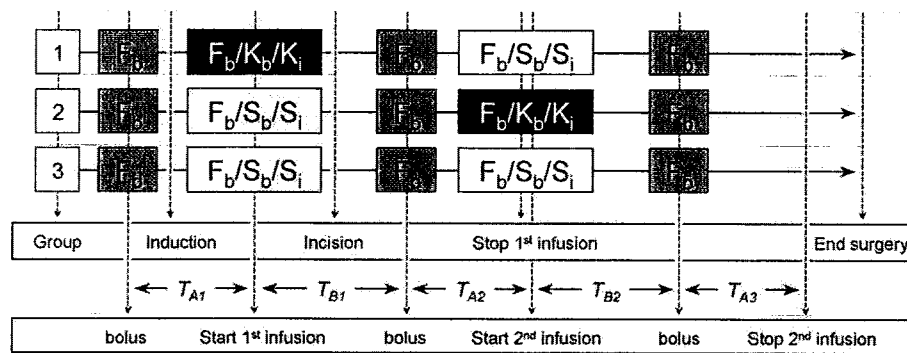


Fig. 1. Flow chart showing timing of drug administration relative to specific pre-operative and intraoperative events. To ensure comparability among groups, time intervals T_{A1} , T_{A2} , T_{A3} and T_{B1} , T_{B2} were designed to be of equal duration, respectively. See Table 1 for actual duration of each interval. Abbreviations: F, fentanyl; K, ketamine; S, saline; subscript b, bolus; subscript i, infusion.

saline and ketamine (1 mg ml^{-1}) for group 2, and saline and saline for group 3.

All patients received i.v. fentanyl ($1 \mu\text{g kg}^{-1}$, $25 \mu\text{g ml}^{-1}$) every 80 min starting approximately 5 min before induction of general anesthesia (Fig. 1 and Table 1). Approximately 10 min before skin incision, and after induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl ($0.5 \mu\text{g kg}^{-1}$). This was followed immediately by an i.v. bolus dose (0.2 ml kg^{-1}) and an i.v. infusion ($0.0025 \text{ ml kg}^{-1} \text{ min}^{-1}$) from the first syringe labeled 'pre-incision'. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl ($0.5 \mu\text{g kg}^{-1}$). This was followed immediately by an i.v. bolus dose (0.2 ml kg^{-1}) and an i.v. infusion ($0.0025 \text{ ml kg}^{-1} \text{ min}^{-1}$) from the second syringe labeled 'post-incision'. The second infusion was stopped after 80 min, approximately 150 min after incision.

2.5.3. General anesthesia

Patients received midazolam 1–2 mg i.v. as pre-medication approximately 1 h before surgery. General anesthesia was induced with thiopental $4\text{--}6 \text{ mg kg}^{-1}$. Intubation followed the administration of d-tubo curarine ($3.0\text{--}4.5 \text{ mg}$) and succinylcholine $1.0\text{--}1.5 \text{ mg kg}^{-1}$. General anesthesia was maintained with 60% N_2O in O_2 and isoflurane. Pancuronium was used for neuromuscular blockade. Vasoactive agents (beta-blockers, vasodilators and vasopressors) were used as required to maintain

hemodynamic parameters within $\pm 20\%$ of mean pre-operative baseline values. At the conclusion of the surgery, neuromuscular blockade was reversed with neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.02 mg kg^{-1} . The trachea was extubated after emergence and upon resumption of spontaneous breathing. Patients received supplemental O_2 by mask and were transported to the post-anesthetic care unit (PACU).

2.5.4. Intraoperative monitoring

All patients were continuously monitored with an arterial line (systolic, mean, diastolic blood pressure), electrocardiogram (heart rate and rhythm), pulse oximeter, nasal temperature probe, and end-tidal monitor (anaesthetic gas and carbon dioxide levels). Intra-operative hemodynamics and end-tidal isoflurane were recorded every minute for the first 5 min after skin incision and every 15 min thereafter until the end of surgery.

2.5.5. Postoperative analgesia

Patients were assessed immediately upon arrival in the PACU and were connected to a PCA pump system (Abbott Life Care Infuser, Abbott Laboratories, Chicago, IL, USA). If patients complained of pain, a research nurse blind to group allocation administered a loading dose of 2–4 mg morphine. Every 5 min, patients were asked whether they were in need of pain relief. An affirmative response was followed by a 1.0–1.5 mg i.v. bolus of morphine.

Table 1
Timing of drug administration relative to intraoperative events (mean \pm SD)

Time interval (see Fig. 1)	Interval between intraoperative events	Group 1	Group 2	Group 3
–	Min between pre-induction dose of fentanyl and induction of GA	4.6 ± 3.7	4.8 ± 3.9	4.8 ± 3.5
T_{A1}	Min between pre-induction dose of fentanyl and start of infusion 1	22.6 ± 6.1	25.1 ± 7.0	23.2 ± 8.2
–	Min between start of infusion 1 and incision	9.9 ± 6.4	9.2 ± 2.6	9.7 ± 3.3
T_{B1}	Min between start of infusion 1 and 1st post-incisional dose of fentanyl	58.6 ± 3.8	58.9 ± 3.4	59.4 ± 3.3
T_{A2}	Min between 2nd post-incisional dose of fentanyl and start of infusion 2	22.6 ± 6.7	25.4 ± 7.3	23.2 ± 8.2
T_{B2}	Min between start of infusion 2 and 3rd post-incisional dose of fentanyl	58.2 ± 5.2	59.0 ± 4.0	59.4 ± 3.3
T_{A3}	Min between 3rd post-incisional dose of fentanyl and end of infusion 2	23.1 ± 7.8	26.6 ± 17.8	23.0 ± 8.4
$T_{B1} + T_{A2}$	Duration in min of first infusion	81.2 ± 8.3	84.2 ± 7.9	82.6 ± 8.3
$T_{B2} + T_{A3}$	Duration in min of second infusion	81.3 ± 8.0	85.5 ± 17.7	82.4 ± 8.8

This procedure was repeated until the patients were alert enough to begin self-administration using the PCA pump button. The PCA pump was set to deliver a 1.0–1.5 mg i.v. bolus dose of morphine with a lock-out time of 5 min, a maximum dose of 40 mg in any 4 h period, and no continuous background infusion. This regimen was overseen by the Acute Pain Service and was continued on the ward for 72 h during which time no other analgesics were administered. Morphine consumption in milligrams was calculated on an hourly basis from hard copy records (Abbott TRW Printer, Model TP 40, Abbott Laboratories, Chicago, IL, USA) of the 72 h study period.

2.5.6. Measurement of post-operative pain and von Frey thresholds

VAS-R was measured 3, 6, 12, 24, 48, and 72 h after surgery. VAS-M, MPQ, von Frey TT and PT were measured at 24, 48, and 72 h after surgery.

2.5.7. Two-week follow-up

Patients were seen in the hospital on their first visit post-discharge approximately 2 weeks after surgery. An assessment of pain status since discharge was obtained and von Frey touch (TT) and pain (PT) thresholds were measured as previously described.

2.5.8. Six-month follow-up

Patients were contacted by telephone approximately 6 months from the date of surgery and administered the post-surgical follow-up questionnaire. A maximum of five attempts was made to contact each patient by telephone.

2.5.9. Sample size calculation

Sample size estimation was performed using data from an earlier study of men undergoing radical prostatectomy who received pre-incisional or post-incisional lumbar epidural bupivacaine (Katz et al., 1994). In that study, mean cumulative PCA morphine was 55 mg for the pre-incisional group and 71 mg for the post-incisional group with a standard deviation of 28 mg. The 16 mg difference in morphine consumption represented a savings of 30% in favor of the pre-incisional group. Using a type I error rate of 0.05 we estimated that we would require 45 patients per group to detect a mean difference of 16 mg (SD 28 mg) with a power of ~80% (Brown et al., 1993). Two Monte Carlo simulations (Hammersley and Handscomb, 1964) of 10,000 trials each were then performed under the following two conditions assuming 45 patients per group and a standard deviation of 28 mg: (1) pre-incision mean 55 mg, post-incision mean 71 mg, control mean 85 mg; and (2) pre-incision mean 55 mg, post-incision mean = control mean = 71 mg. Comparisons between pairs of means were undertaken when the omnibus *F*-test was statistically significant (i.e. $\alpha = 0.05$, two tailed). The Monte Carlo simulations indicated that a sample size of 45 patients per

group provided a power of 80% under condition 1 and 99% under condition 2.

2.5.10. Data entry and verification

Data were keyed in twice. One of the data sets was checked for errors manually by two research assistants/nurses. After correcting any errors, the two data sets were compared field by field by an in-house computer program. Discrepancies between matching records in the two data sets were corrected by referring back to the raw data.

2.5.11. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, release 11.0.1, Chicago, IL) and Primer of Biostatistics: The Program (Version 4.0, McGraw Hill, New York, NY, USA) (Glantz, 1997). Background demographic data and clinical variables were compared using ANOVA for parametric data and χ^2 -test for nominal data.

Primary outcome variable. Cumulative morphine consumption at 72 h after surgery was analyzed by one-way ANOVA followed by directional comparisons between pairs of means.

Secondary outcome variables. Visual analogue pain scores at rest (VAS-R), after movement (VAS-M) and von Frey touch (TT) and pain thresholds (PT) were analyzed by 2-way between-within ANOVA using group as the between subjects factor and time after surgery as the within subjects factor. The regression lines relating time and cumulative morphine consumption on day 3 after surgery (between 49 and 72 h) were compared pair wise by one-way ANOVA by first testing the overall coincidence of the regression lines (Glantz, 1997). If the overall coincidence differed, the slopes and intercepts were compared by *t*-test using the Bonferroni type I error rate correction for multiple comparisons ($\alpha = 0.05/\text{number of comparisons}$). MPQ pain rating indexes (PRIs) and MPQ present pain intensity (PPI) were analyzed by non-parametric Kruskal–Wallis ANOVA of ranks. MHI and STAI-S scores were analyzed by one-way ANOVA.

All data presented are mean \pm SD unless otherwise specified. $P \leq 0.05$ is considered statistically significant.

3. Results

3.1. Recruitment and patient withdrawals

Between June 1994 and October 1997, 168 patients were recruited into the study. In total 25 patients were withdrawn for the following reasons.

Pre-randomization dropouts ($n = 8$): Procedure cancelled on the day of surgery ($n = 2$); pharmacy did not prepare the drugs in time for the surgery ($n = 2$); personnel not available to run the case ($n = 4$).

Intraoperative withdrawals ($n = 10$): Excessive bleeding and/or change in operative procedure ($n = 4$);

administration of additional analgesic agents ($n = 3$); problems with the infusion pump ($n = 2$); anaphylactic reaction to general anaesthesia ($n = 1$).

Postoperative withdrawals ($n = 7$): bleeding ($n = 1$); faulty PCA equipment ($n = 1$); severe bladder spasms requiring additional analgesics ($n = 3$); alcohol withdrawal/delirium tremens ($n = 1$); excessive drowsiness precluding data collection ($n = 1$).

There were no significant differences among groups in the proportion of patients withdrawn ($n = 7, 6,$ and 4 for groups 1–3, respectively).

In total, 143 patients completed the study; 47 in group 1, 50 in group 2 and 46 in group 3.

3.2. Timing of drug administration relative to intraoperative events

Table 1 and Fig. 1 show the intervals between specific intraoperative events as they relate to the time of administration of fentanyl, ketamine and saline. As designed, there were no significant group differences between any of the intervals, including, the time between the pre-induction dose of fentanyl and induction, the time between the start of the first infusion and incision, and the duration of the first and second infusions.

3.3. Demographic, psychosocial and intraoperative variables

There were no significant differences among the groups in demographic or clinical data (Table 2) or pre-operative MHI and STAI-S scores (Table 3). The groups did not differ significantly in the total dose of i.v. fentanyl. Groups 1 and 2 did not differ significantly in the total dose of ketamine received.

Figs. 2 and 3 show mean percent end tidal isoflurane and the mean change from pre-operative baseline level in heart rate and mean blood pressure across the surgical procedure. There were no significant differences among the three groups in any of these parameters.

Table 2
Demographic and clinical variables

Demographic/ clinical measure	Group 1	Group 2	Group 3
Age (years)	62 ± 5.8	62 ± 6.2	61 ± 6.7
Height (cm)	175 ± 8.3	178 ± 7.9	176 ± 6.1
Weight (kg)	81 ± 9.5	84 ± 17.1	84 ± 16.8
Frequency of ASA status (1:2)	25:21	18:32	23:23
Surgery duration (min)	180 ± 30.9	181 ± 30.7	182 ± 45.2
Blood loss (ml)	1507 ± 983.5	1770 ± 1217.7	1603 ± 1015.7
Total fentanyl (µg)	364.8 ± 59.66	365.1 ± 61.84	369.9 ± 87.24
Total ketamine (mg)	31.9 ± 4.21	32.2 ± 3.9	0.0 ± 0.0

Data are mean ± SD unless otherwise stated.

Table 3
Scores (mean ± SD) on the Spielberger State Anxiety Inventory (STAI-S) and Mental Health Inventory (MHI) obtained the evening before surgery

Psychosocial measure	Group 1	Group 2	Group 3
STAI-S	38.1 ± 9.63	35.8 ± 10.87	34.8 ± 8.77
MHI-anxiety	24.4 ± 3.33	24.2 ± 4.42	25.4 ± 3.63
MHI-depression	20.9 ± 2.40	21.1 ± 3.28	21.5 ± 2.70
MHI-loss of control	22.1 ± 2.12	22.1 ± 1.95	22.2 ± 1.94
MHI-positive affect	18.7 ± 3.09	18.4 ± 3.12	19.3 ± 2.34
MHI-total score	91.5 ± 10.45	91.3 ± 11.64	93.9 ± 9.04

3.4. PCA morphine consumption

Although cumulative PCA morphine consumption at 72 h was lower in group 1 (92.3 ± 45.9 mg) than group 2 (107.2 ± 58.4 mg) and group 3 (103.6 ± 50.4 mg), comparisons between the means did not reach the conventional 0.05 level of significance ($P = 0.08$ for groups 1 vs. 2 and $P = 0.08$ for groups 1 vs. 3). The number of PCA requests that did not result in a bolus of morphine (i.e. requests made during the 5-min lock-out period) did not differ significantly among the groups (data not shown). Table 4 shows PCA morphine consumption between intervals when pain at rest was assessed. Morphine consumption did not differ significantly during any of the intervals.

Fig. 4 shows cumulative morphine consumption for the three groups across the 72 h study period. Also shown are the best-fitting linear regression lines relating cumulative morphine consumption and time for each group across the final 24 h period (day 3, 49–72 h). On day 3, the hourly rate (mean ± SEM) of morphine consumption in group 1 (0.61 ± 0.013 mg h⁻¹) was significantly lower ($P < 0.0009$) than that in group 2 (0.86 ± 0.011 mg h⁻¹) and group 3 (0.89 ± 0.008 mg h⁻¹). Groups 2 and 3 did not differ significantly.

3.5. Postoperative pain and von Frey thresholds

There were no significant differences among the groups in VAS pain scores (Fig. 5), MPQ pain rating indexes

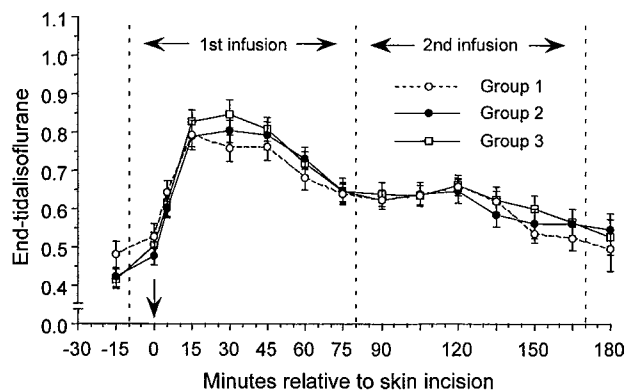


Fig. 2. Percent end-tidal isoflurane shown for the three groups during the first and second intraoperative i.v. infusions. Downward pointing arrow at zero on the X-axis corresponds to time of skin incision.

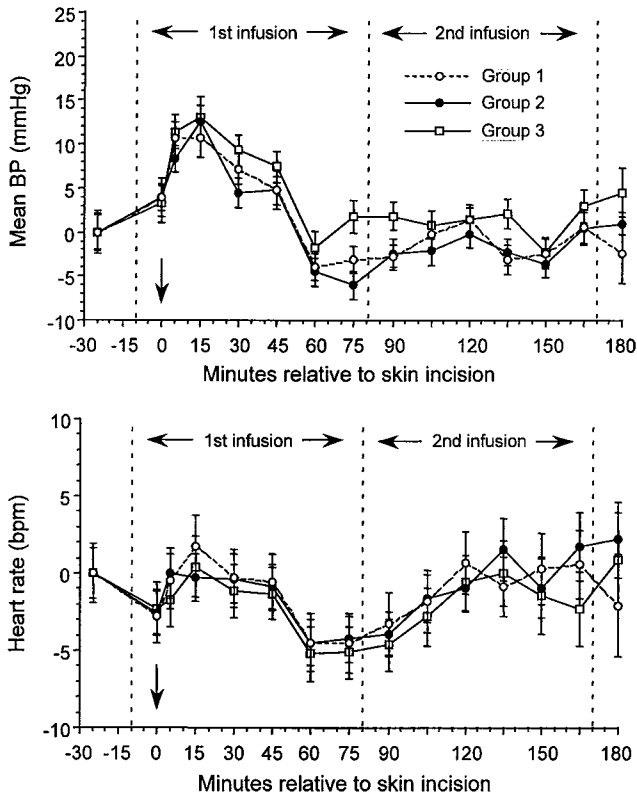


Fig. 3. Change from baseline in mean blood pressure and heart rate shown for the three groups during the first and second intraoperative i.v. infusions. Downward pointing arrow at zero on the X-axis corresponds to time of skin incision.

(Table 5), or von Frey touch or pain thresholds measured near the wound and at the control site on the inner forearm (Fig. 6).

3.6. Complications/adverse events

The following complications/adverse events occurred intraoperatively: excessive bleeding in two patients (one in group 1 and one in group 3); anaphylactic reaction to the general anesthetic in one patient (group 2). The following complications/adverse events occurred post-operatively: vivid dreams in one patient (group 2); agitation in two patients (one in group 1 and one in group 3); drowsiness in

Table 4
PCA morphine consumption (mg) within intervals bounded by times when pain at rest was assessed

Time interval after surgery (h)	Group 1	Group 2	Group 3
0-3	14.5 ± 7.9	14.7 ± 9.1	15.2 ± 7.4
3-6	5.7 ± 5.0	7.4 ± 5.4	5.7 ± 3.9
6-12	7.8 ± 4.9	9.1 ± 7.1	8.7 ± 6.6
12-24	20.2 ± 11.3	24.1 ± 15.2	22.7 ± 14.9
24-48	28.1 ± 16.4	30.1 ± 20.1	29.8 ± 17.3
48-72	16.0 ± 15.7	21.7 ± 20.0	21.5 ± 18.9

Data are mean ± SD.

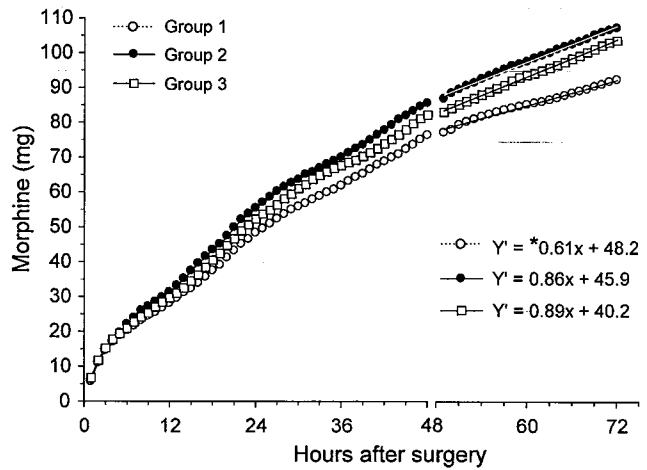


Fig. 4. An hour-by-hour plot of cumulative PCA morphine consumption for each group showing the best-fitting, least squares regression line calculated for day 3 (49-72 h after surgery). Each regression line accounts for at least 95% (r^2) of the total variance. The hourly rate of morphine consumption on day 3 was significantly lower for groups 1 vs. 2 and for groups 1 vs. 3 reflecting the benefit of pre-operative ketamine. Bonferroni corrected significance tests of the regression line slope comparing groups 1 vs. 2 and groups 1 vs. 3 on day 3, $*P < 0.0009$.

two patients (group 1); alcohol withdrawal/delirium tremens in one patient (group 2); and hypotension and bleeding in one patient (group 3).

3.7. Two-week follow-up assessment

One hundred and twenty-five of the 143 patients (87.4%) were assessed at the hospital approximately 2 weeks after discharge ($n = 40, 43,$ and 42 in groups 1-3, respectively). The overall incidence of pain was 55.2% ($n = 79$). The pain intensity was in the mild to moderate range. von Frey touch and pain thresholds are shown in Fig. 6. There were no significant differences among the three groups in any of the variables measured (Table 6).

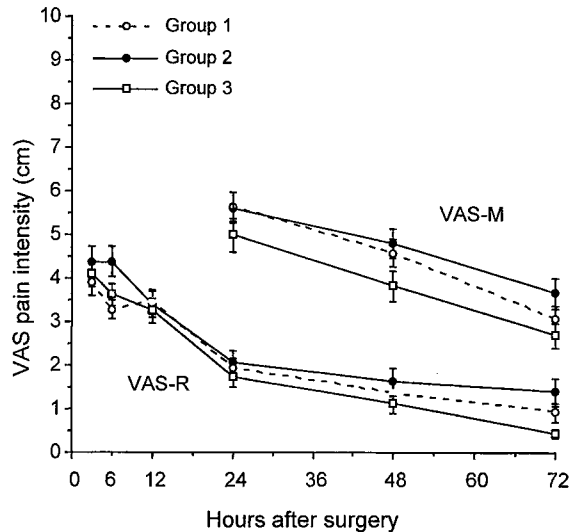


Fig. 5. Visual analogue scale (VAS) pain scores at rest (R) and after standardized movement (M). Data are mean and standard deviation.

Table 5

McGill Pain Questionnaire (MPQ) pain rating index (PRI) for sensory (S), affective (A), evaluative (E), miscellaneous (M) and total (T) scores, present pain intensity (PPI) and number of words chosen (NWC)

MPQ scores	Day 1 (24 h) post-op			Day 2 (48 h) post-op			Day 3 (72 h) post-op		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
PRI-S	8.0 ± 7.0	6.9 ± 7.1	7.6 ± 6.3	6.2 ± 7.0	4.4 ± 5.2	4.4 ± 4.8	4.0 ± 5.7	4.4 ± 5.3	2.6 ± 4.0
PRI-A	0.7 ± 1.1	0.7 ± 1.2	0.7 ± 1.5	0.8 ± 2.1	0.7 ± 1.4	0.4 ± 1.0	0.3 ± 0.7	0.3 ± 0.7	0.1 ± 0.3
PRI-E	1.1 ± 1.2	0.9 ± 1.2	1.0 ± 1.3	0.9 ± 1.4	0.5 ± 0.8	0.5 ± 1.0	0.6 ± 1.1	0.6 ± 1.1	0.2 ± 0.5
PRI-M	1.7 ± 2.5	1.4 ± 2.0	1.7 ± 2.2	1.2 ± 1.9	1.6 ± 2.6	1.1 ± 2.2	0.6 ± 1.4	0.5 ± 0.8	0.5 ± 1.0
PRI-T	11.5 ± 10.1	9.9 ± 10.4	11.1 ± 9.5	9.1 ± 11.4	7.2 ± 8.6	6.5 ± 7.1	5.5 ± 7.8	5.9 ± 7.1	3.3 ± 5.1
PPI	1.3 ± 0.8	1.3 ± 0.9	1.4 ± 0.9	1.2 ± 1.3	1.0 ± 1.1	1.1 ± 1.0	0.7 ± 0.9	0.9 ± 1.0	0.6 ± 0.8
NWC	7.0 ± 5.9	5.7 ± 5.6	6.3 ± 4.9	5.8 ± 7.3	4.0 ± 4.5	3.8 ± 4.1	3.3 ± 4.8	3.8 ± 4.8	1.9 ± 2.8

Data are mean ± SD.

3.8. Six-month follow-up interview

One hundred and eight of the 143 patients (75.5%) were reached by telephone 6 months after surgery ($n = 34, 36,$ and 38 in groups 1–3, respectively). The groups did not differ significantly in the most intense pain they remembered having experienced after surgery (Table 7) which was a remarkably accurate reflection of their 24 h VAS-M pain scores (Fig. 5).

The overall incidence of pain was 10.5% ($n = 15$) with no significant difference among the three groups (Table 7). The pain was described as sharp, burning or aching and as originating in deep tissue and at the scar. In general, the intensity of pain was mild and all 15 patients reported not taking analgesic medication for the pain. One patient in group 2 reported that the pain interfered 'slightly' with his everyday activities; the remaining 14 reported no interference at all.

4. Discussion

The results of the present study do not support the hypothesis that pre-operative i.v. administration of the NMDA receptor antagonist ketamine results in a clinically meaningful reduction in pain or morphine consumption when compared with a saline control condition or post-incisional administration of i.v. ketamine. In the present study, a bolus dose of 0.2 mg kg^{-1} ketamine followed by continuous infusion of $2.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$ for 80 min was started 10 min before or 70 min after incision. This amounted to approximately 30 mg ketamine administered over the duration of the 3-h procedure. There was no evidence that post-operative pain or analgesic use differed as a function of pre-operative or post-incisional administration of ketamine. Nor did this regimen reduce post-operative cumulative morphine consumption or pain compared with a saline control group that did not receive ketamine.

However, between group comparisons of the regression line slopes relating morphine and time support the idea that

pre-operative ketamine is associated with a late reduction in the rate of morphine consumption beginning at 49 h after surgery and extending to the end of the study, 72 h after surgery. The difference in the rate of morphine consumption between group 1 and the other two groups on day 3 was approximately 0.25 mg h^{-1} (Fig. 4) amounting to 6 mg less of morphine over 24 h. Since this effect was observed two days after ketamine administration (>15 ketamine half lives; Clements et al., 1982) in groups 1 and 2, it is likely not related to the ongoing actions of the drug but rather to a possible reduction in central sensitization.

The difference in the rate of morphine consumption in favor of the pre-incisional group supports the idea that early and late noxious intraoperative stimuli contribute differentially to the establishment of central sensitization (Katz, 2003; Katz et al., 2003). In the present study, it appears that the noxious events during the early intraoperative period including incision and the following 70 min contribute to a greater extent to central sensitization than do noxious late intraoperative or post-operative stimuli. Furthermore, given the absence of a difference in rate of morphine consumption between groups 2 and 3, it would appear that the most

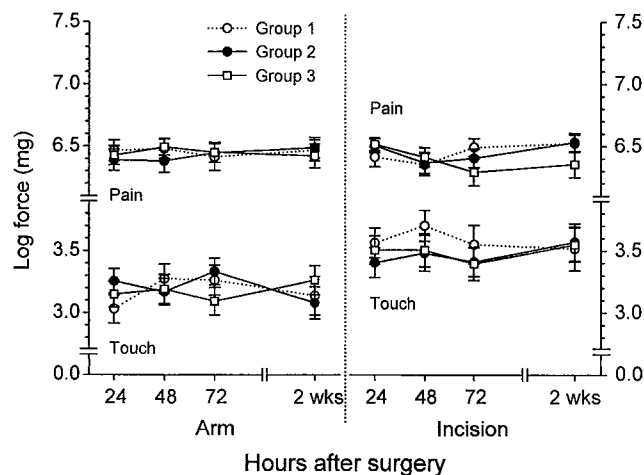


Fig. 6. von Frey touch and pain thresholds obtained 10 cm from the wound dressing and at a control site on the forearm. Data are mean and standard deviation.

Table 6

Data [*n* (%)] from 2-week post-discharge follow-up

Follow-up measure	Group 1	Group 2	Group 3
Days since surgery (mean \pm SD)	18.9 \pm 4.4	19.7 \pm 10.7	19.6 \pm 4.6
VAS pain at rest (mean \pm SD)	2.8 \pm 1.5	3.0 \pm 1.7	2.9 \pm 1.9
Pain-free on discharge (%)	25 (62.5)	24 (55.8)	25 (61.0)
Pain since discharge (%)	23 (57.5)	30 (69.8)	26 (63.4)
Scar tender to touch (%)	21 (52.5)	23 (53.5)	22 (53.7)

important contribution to central sensitization in the present study originates in the effects of the barrage of noxious impulses arising from incision and subsequent noxious events. Nevertheless, the clinical significance of this effect is small and the somewhat lower morphine consumption was not accompanied by differences in pain hypersensitivity as measured by von Frey filaments, by pain scores at rest or after mobilization, or in the incidence and intensity of pain 2 weeks and 6 months after surgery.

The present design thus compared an early vs. late intraoperative start to NMDA receptor blockade by a low dose of ketamine. The timing of administration of the ketamine infusions and total dose of ketamine were designed to reduce the incidence of adverse reactions. Because of reports of psychotomimetic and emergence reactions associated ketamine (Sethna et al., 1998; White et al., 1982), we planned to stop the second infusion approximately 20–30 min before the end of surgery so as to minimize the potential occurrence of these adverse effects, especially in group 2 patients. We anticipated the mean duration of the radical prostatectomy procedure to be 3 h as in our earlier study (Katz et al., 1994) so that running the two infusions for approximately 80 min each translated into

Table 7

Six-month follow-up data

Follow-up measure	Group 1	Group 2	Group 3
Follow up time in days	201.8 \pm 17.8	204.7 \pm 19.3	205.2 \pm 25.2
Most intense pain after surgery			
PPI (0–5)	2.1 \pm 0.6	2.1 \pm 0.7	2.0 \pm 0.9
VRS (0–10)	5.1 \pm 1.9	5.6 \pm 2.2	5.1 \pm 2.5
Has pain at site of surgery [<i>n</i> (%)]	6 (17.6)	2 (5.6)	7 (8.4)
Taking medication [<i>n</i>]	0	0	0
Pain interference in daily activities			
Not at all [<i>n</i> (%)]	6 (100)	1 (50)	7 (100)
Slightly [<i>n</i> (%)]	0 (0)	1 (50)	0 (0)
VAS-rest pain	2.3 \pm 1.2	2.8 \pm 1.1	3.4 \pm 3.0
McGill Pain Questionnaire scores			
PRI-sensory	2.4 \pm 2.1	2.0 \pm 1.4	3.9 \pm 2.7
PRI-affective	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
PRI-evaluative	0.6 \pm 0.5	1.0 \pm 0.0	0.4 \pm 0.5
PRI-total	3.0 \pm 2.1	3.0 \pm 1.4	4.9 \pm 2.8
Present pain intensity	1.4 \pm 0.5	1.0 \pm 0.0	1.7 \pm 1.5
Number of words chosen	2.2 \pm 1.3	2.5 \pm 0.7	3.1 \pm 1.5

Follow-up time and most intense pain are reported for all 108 patients reached. The remaining variables show data only for patients reporting pain. Data are mean \pm SD unless otherwise stated.

stopping the second infusion on average 30 min before the end of surgery (Table 1 and Fig. 1). Emergence reactions were not observed; nor were hallucinations or other psychotomimetic effects although one patient in group 2 reported having had vivid dreams.

The low dose of ketamine also appeared to have no effect on intraoperative heart rate or blood pressure in contrast to the results reported by Roytblat et al. (1993) showing a marked reduction in intraoperative hemodynamics associated with a single pre-operative bolus dose of 0.15 mg kg⁻¹ ketamine i.v. As shown in Figs. 2 and 3 isoflurane requirements and hemodynamic responses did not significantly differ among the three groups, nor between the first and second infusions within groups 1 and 2. To our knowledge, the only other study to compare low dose ketamine (0.15 mg kg⁻¹) and saline also reported no significant differences in intraoperative heart rate and blood pressure (Hirata et al., 1995).

There are several possibilities that alone, or in various combinations, may explain the lack of a clinically significant pre-emptive or preventive effect of the fentanyl and ketamine used in the present study. The first has to do with the related issues of timing of ketamine administration relative to incision and duration of NMDA receptor blockade. Central sensitization is not only induced during surgery but also post-operatively by inflammatory inputs (Katz, 2003; Kissin, 2000). As discussed above, neither group 1 nor group 2 received the ketamine infusion for the duration of the surgical procedure and no ketamine was given in the post-operative period. Thus, the modest effects in rate of morphine consumption we observed might have been enhanced had we started the infusion before surgery and continued it throughout the procedure into the post-operative period.

Secondly, the dose of ketamine used in the present study may have been too small. Studies of abdominal surgery patients have reported significant effects using bolus doses that ranged between 0.15 and 2 mg kg⁻¹ and infusion rates between \sim 8 and 20 μ g kg⁻¹ min⁻¹ (Aida et al., 2000; Fu et al., 1997; Kee et al., 1997; Roytblat et al., 1993; Tverskoy et al., 1994). Negative results have also been reported after abdominal hysterectomy using a total ketamine dose approximating the 30 mg used in the present study (Wildner-Smith et al., 1998). Other surgical procedures have produced mixed results: the same small bolus dose of 0.15 mg kg⁻¹ ketamine produced an early opposite effect in favor of the post-incision group after mastectomy (Adam et al., 1999) and significantly lower post-operative morphine requirements 48 h after anterior cruciate ligament repair in patients treated with ketamine before or after surgery compared with a placebo control group (Menigaux et al., 2000). In addition, a considerable amount of blood loss occurred in all three groups (Table 2) which, together with the associated fluid management, may have reduced further the ketamine serum concentration in groups 1 and 2. It is possible that a larger dose of ketamine combined with

a continuous intravenous infusion would have resulted in more clinically significant results in the present study.

A third reason for the lack of a clinically significant effect may have to do with the co-administration of fentanyl with ketamine and more generally, the role of ketamine in potentiating opioid analgesia by preventing or reducing central sensitization. Our expectation was that adding low-dose ketamine to a standard general anesthetic regimen using fentanyl would produce enhanced antinociceptive effects due to the combined actions of the two agents operating at different receptor sites (Chapman and Dickenson, 1992; Dickenson, 1997), and in particular by preventing or obtunding the NMDA-mediated state of pain hypersensitivity that normally ensues following tissue damage (Dickenson, 1997). However, the results of a recent rat study in which epidural ketamine was combined with various doses of morphine and fentanyl suggests that the effects of ketamine may depend on the specific mu opioid agonist (Hoffmann et al., 2003). Whereas ketamine potentiated the antinociceptive effects of morphine, it antagonized the effects of fentanyl at several doses. The mechanism by which this antagonistic effect occurred is not known but may involve competition for active blood-brain barrier transport proteins due to the high lipophilicity of both ketamine and fentanyl, competition between ketamine and fentanyl for the mu receptor, drug differences in mu receptor subtype binding, or intracellular differences in phosphorylation associated with specific opioid-ketamine combinations (Hoffmann et al., 2003).

To date six studies have evaluated pre-emptive or preventive effects of i.v. ketamine in combination with an opioid. The clinical data do not point to a clear-cut relationship between the relative efficacy of ketamine when administered with various opioid agonists although Hoffmann et al. (2003) suggested that lipophilicity may be a factor. The two studies that administered ketamine in combination with morphine found a significant opioid sparing effect (Aida et al., 2000; Kee et al., 1997), and a significant reduction in post-operative pain (Aida et al., 2000) compared with a control group. The only other study to have administered pre-operative ketamine with fentanyl also found a significant opioid sparing effect in favor of the ketamine treated patients compared with a saline control group (Roytblat et al., 1993). The remaining three studies did not find a pre-emptive or preventive effect when ketamine was administered in combination with the fast-acting opioids sufentanil (Adam et al., 1999; Menigaux et al., 2000) or alfentanil (Dahl et al., 2000). Interestingly, co-administration of ketamine and alfentanil before or after surgery resulted in *greater* pain intensity when compared with a saline control group that received alfentanil alone (Dahl et al., 2000). These results were opposite in direction to what was predicted, and are consistent with the suggestion that ketamine may have antagonized the antinociceptive effects of the opioid (Hoffmann et al., 2003). Further studies are required to determine the relative

efficacy of ketamine in combination with various opioid agonists.

The literature contains two competing hypotheses that may, in part, help to explain the negative findings of the present study. On the one hand, it is possible that the fentanyl and other agents (e.g. nitrous oxide), administered as part of the general anesthetic regimen, exerted subtle, additive pre-emptive effects, which may have attenuated the central sensitizing effects of surgery in all patients thereby minimizing the effect size when comparing groups 1 and 2 with the control group.

On the other hand, recent evidence shows that under certain conditions opioids activate pronociceptive systems associated with acute opioid tolerance and opioid-induced hyperalgesia (Celerier et al., 2000; Crain and Shen, 2000; Kissin et al., 2000; Mao et al., 1995). These phenomena are derived from an NMDA-receptor mediated mechanism similar to that which occurs following tissue damaging injury. Mu-opioid receptor agonists produce a sustained increase in NMDA-activated currents by activating intracellular protein kinase C which potentiates the NMDA response by reducing the voltage-dependent Mg^{2+} block of NMDA-receptor channels. In rats, pre-treatment with ketamine prior to opioid administration and followed by repeated ketamine injections prevented opioid-induced hyperalgesia and acute tolerance to opioids (Laulin et al., 2002). It is possible that administration of fentanyl to all patients may have activated a pronociceptive system thereby minimizing later inter-groups differences in post-operative pain and morphine consumption. The subsequent administration of ketamine to groups 1 and 2 after the fentanyl may have been too late to prevent opioid-induced NMDA-receptor activation.

Taken together, these results suggest that clinically significant reductions in post-operative pain and analgesic use are more likely to be found when ketamine is administered preventively (Katz, 2003; McCartney et al., 2004) before induction of anesthesia (prior to an opioid; preferably morphine) and continuously throughout the operation. In addition, use of the S(+) isomer of ketamine may produce more substantial results. The S(+) isomer has been shown to be 3–4 times more potent than the R(+) isomer in producing anti-nociceptive effects and, in equianalgesic doses, possibly to induce fewer psychotomimetic effects (Marietta et al., 1977; Mathisen et al., 1995; White et al., 1985). These suggestions appear to be supported by preliminary results (Snijdelaar et al., 2004).

In summary, pre-operative i.v. fentanyl plus a low-dose i.v. ketamine infusion did not reduce cumulative morphine consumption or pain, to a clinically significant extent, when compared with the same regimen initiated 70 min after the start of surgery or a fentanyl plus saline control condition. Although the rate of morphine consumption on day 3 was significantly lower in group 1 than in groups 2 and 3, by 2 weeks and 6 months after surgery the three groups did not differ significantly in pain incidence or intensity. Extending

the duration of the infusion to cover a longer period of nociceptive activity, use of the S(+) isomer of ketamine, and co-administering it in combination with morphine may produce more clinically meaningful results.

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