 

# *Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine*

*Vincent Joly, M.D.,* Philippe Richebe, M.D.,† Bruno Guignard, M.D.,* Dominique Fletcher, M.D.,‡ Pierre Maurette, M.D.,§ Daniel I. Sessler, M.D.,‖ Marcel Chauvin, M.D.#*

***Background:*** **Remifentanil-induced secondary hyperalgesia has been documented experimentally in both animals and healthy human volunteers, but never clinically. This study tested the hypotheses that increased pain sensitivity assessed by periincisional allodynia and hyperalgesia can occur after relatively large-dose intraoperative remifentanil and that small-dose ketamine prevents this hyperalgesia.**

***Methods:*** **Seventy-five patients undergoing major abdominal surgery were randomly assigned to receive (1) intraoperative remifentanil at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (small-dose remifentanil); (2) intraoperative remifentanil at 0.40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (large-dose remifentanil); or (3) intraoperative remifentanil at 0.40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.5 mg/kg ketamine just after the induction, followed by an intraoperative infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until skin closure and then 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 48 h (large-dose remifentanil–ketamine). Pain scores and morphine consumption were recorded for 48 postoperative hours. Quantitative sensory tests, peak expiratory flow measures, and cognitive tests were performed at 24 and 48 h.**

***Results:*** **Hyperalgesia to von Frey hair stimulation adjacent to the surgical wound and morphine requirements were larger ($P < 0.05$) and allodynia to von Frey hair stimulation was greater ($P < 0.01$) in the large-dose remifentanil group compared with the other two groups, which were comparable. There were no significant differences in pain, pressure pain detection threshold with an algometer, peak flow, cognitive tests, or side effects.**

***Conclusion:*** **A relatively large dose of intraoperative remifentanil triggers postoperative secondary hyperalgesia. Remifentanil-induced hyperalgesia was prevented by small-dose ketamine, implicating an *N*-methyl-D-aspartate pain-facilitator process.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Attending Anesthesiologist, Department of Anesthesia, ‡ Professor, # Professor and Chair, Department of Anesthesia and Institut National de la Santé et de la Recherche Médicale (INSERM) E 332, Hôpital Ambroise Pare, Assistance Publique Hôpitaux de Paris. † Assistant Professor, § Professor and Chair, Department of Anesthesia 3, Hôpital Pellegrin. ‖ Vice Dean for Research and Associate Vice President for Health Affairs, Director OUTCOMES RESEARCH Institute, and Interim Chair and Lolita & Samuel Weakley Distinguished Professor of Anesthesiology, University of Louisville.

Received from the Department of Anesthesia and INSERM E 332, Hôpital Ambroise Pare, Assistance Publique–Hôpitaux de Paris, Boulogne, France; the Department of Anesthesia, Hôpital Pellegrin, Bordeaux, France; and the OUTCOMES RESEARCH Institute and Department of Anesthesiology & Perioperative Medicine, University of Louisville, Louisville, Kentucky. Submitted for publication November 12, 2004. Accepted for publication March 15, 2005. Supported by a grant from Délégation Régionale de la Recherche Clinique d'Ile de France for a Hospital Clinical Research Project; grant No. GM 061655 from the National Institutes of Health, Bethesda, Maryland; the Gheens Foundation, Louisville, Kentucky; the Joseph Drown Foundation, Los Angeles, California; and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, Kentucky.

Address reprint requests to Dr. Chauvin: Assistance Publique–Hôpitaux de Paris, 92100 Boulogne, France. Address electronic mail to: marcel.chauvin@apr.ap-hop-paris.fr. On the World Wide Web: www.or.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

OPIOIDS are potent analgesics and are often necessary for treating moderate to severe pain. However, experimental studies report that opioids may also elicit hyperalgesia (increased sensitivity to noxious stimuli) and allodynia (nociceptive responses to innocuous stimulation). Animal studies have demonstrated the development of opioid-induced hyperalgesia.[1–5] In some, opioid-induced hyperalgesia was observed to follow analgesia and lasted long after opioid exposure ended.[1,2,4] In others, though, there was evidence of opioid-induced hyperalgesia during continuous opioid exposure.[3,5] Opioid-induced processes that underlie hyperalgesia decrease antinociception and contribute to opioid tolerance.[3,5,6]

Similar phenomena are probably present when acute opioid tolerance occurs in patients. For example, tolerance to analgesia during 4-h-long constant-rate remifentanil infusions is profound in volunteers and develops within 60–90 min.[7] Moreover, delayed hyperalgesia develops from short-acting opioid exposure,[8–10] and relatively large intraoperative opioid doses are associated with greater postoperative opioid consumption and higher pain scores.[11,12] However, unlike the experimental conditions in which changes in baseline nociceptive thresholds are measured in a controlled setting, it is often difficult to determine whether pain sensitivity changes in response to opioid administration in clinical situations.

Mechanical hyperalgesia surrounding the wound in postoperative patients shares the same central neuronal mechanism as heat-induced secondary hyperalgesia and confirms a degree of central sensitization.[13] Also, it is possible to use periincisional mechanical allodynia and hyperalgesia as objective measures of opioid-induced hyperalgesia in clinical settings.

Among the potential mechanisms leading to opioid-induced hyperalgesia and antinociceptive tolerance, *N*-methyl-D-aspartate (NMDA) pain-facilitator processes seem to play a key role.[14,15] Experimental studies performed in animals and volunteers have shown that NMDA receptor antagonists such as ketamine inhibit central sensitization and prevent opioid-induced hyperalgesia.[1,2,8,16] Previously, we observed that small-dose ketamine was a useful adjuvant to remifentanil-based anesthesia by decreasing intraoperative remifentanil use and postoperative morphine consumption.[17] However, we did not study the action of ketamine and specially the effects of ketamine on remifentanil-induced hyperalgesia in the postoperative setting, which have yet to be evaluated. Therefore, we tested the hypothesis that relatively

large intraoperative doses of remifentanil provoke postoperative hyperalgesia as indicated by periincisional allodynia and hyperalgesia and that small-dose ketamine prevents hyperalgesia.

## Materials and Methods

With approval of the Ethics Committee of the Hôpital Ambroise Paré, adult patients who were scheduled to undergo open colorectal surgery lasting at least 2 h were studied in two centers (Hôpital Ambroise Paré, Boulogne, France, and Hôpital Saint André, Bordeaux, France). All had American Society of Anesthesiologists physical status I–III.

Patients were excluded from the study when (1) immediate extubation was not planned after surgery; (2) they had chronic inflammatory disease including inflammatory bowel disease; (3) they regularly took analgesics or had used opioids within 12 h of surgery; (4) they had a history of drug or alcohol abuse, psychiatric disorder, or obesity (> 130% of ideal body weight); (5) they had contraindications to the self-administration of opioids (*i.e.*, unable to understand the patient-controlled analgesia [PCA] device); or (6) they had a condition, such as a psychiatric disorder, acute cardiovascular disorder, or unstable hypertension, for which the use ketamine was contraindicated.

### *Protocol*

During the preoperative anesthetic evaluation, the evening before surgery, patients were instructed in the use of quantitative sensory tests, the PCA pump (Master PCA; Vial Fresenius, Brezins, France), the peak flow monitor (Mini-Wright; Mediflux, Bry sur Marne, France), a four-point verbal rating scale for pain (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = intense or severe pain), the 100-mm visual analog scale (VAS) for pain (0 = no pain to 100 = worst pain), and an anxiety VAS (0 = no anxiety to 100 = worst imaginable anxiety). Control measures of cognitive function, peak flow, and quantitative sensory tests on skin area of surgery were also performed during this visit. Patients were premedicated with 1 mg lorazepam orally the night before surgery.

Anesthesia was induced with 6 mg/kg thiopental followed by 0.5 mg/kg atracurium to facilitate orotracheal intubation. Two minutes after the thiopental injection, a 1-$\mu$g/kg initial dose of remifentanil was given over 60 s. After tracheal intubation, the patients were ventilated to normocapnia with 50% oxygen and without nitrous oxide. An atracurium infusion was titrated to maintain one twitch in response to a supramaximal train-of-four stimulus at the orbicularis oculi; atracurium was discontinued 15 min before the end of surgery. Anesthesia was maintained with remifentanil per randomized dosing described below and desflurane at an initial end-tidal concentration of 0.5 minimum alveolar concentration (MAC), adjusted to age.[18]

Patients were randomly assigned, in a double-blinded fashion, to one of three groups (25 patients/group). Before the study began, a random-number table was generated, specifying the group to which each patient would be assigned upon entry into the trial. For each patient, an envelope containing the group assignment was prepared, sealed, and sequentially numbered. On the morning of surgery and before induction of anesthesia, a nurse not involved in the evaluation of the patient opened the patient's envelope and prepared remifentanil and ketamine or saline solution syringes. None of the other investigators involved in patient management or data collection were aware of the group assignment. In case of emergency, the attending anesthesiologist was able to break the code. The three treatment groups were as follows:

1. Small-dose remifentanil: Patients were given an intraoperative infusion of remifentanil at a rate of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which has been demonstrated not inducing hyperalgesia in volunteers,[9] and a saline placebo infusion.
2. Large-dose remifentanil: Patients were given an intraoperative infusion of remifentanil at a rate of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, an amount that has been shown to maximally reduce anesthetic requirement during abdominal surgery,[19] and a saline placebo infusion.
3. Large-dose remifentanil–ketamine: Patients were given an intraoperative infusion of remifentanil at a rate of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and ketamine. The dosing scheme for the ketamine infusion was calculated using published pharmacokinetic variables[20] to achieve target plasma concentrations of 250 ng/ml intraoperatively and 100 ng/ml postoperatively. These ketamine concentrations, especially 100 ng/ml, are in the range known to counteract hyperalgesia while producing minimal side effects.[21] The initial loading dose of ketamine, given just after induction, was 0.5 mg/kg; this was followed by a maintenance infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intraoperatively until skin closure and subsequently by an infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the initial 48 postoperative hours.

Insufficient anesthesia was defined as a heart rate that exceeded preinduction values by 15%, systolic arterial blood pressure exceeding baseline values by 20% for at least 1 min, and/or a Bispectral Index of 70 or greater. Patient movement, coughing, tearing, and sweating were also considered signs of inadequate anesthesia. Inspired desflurane concentration was increased stepwise by 1% when insufficient anesthesia was suspected. Hypotension, defined by a systolic arterial pressure less than 80 mmHg or a mean arterial pressure less than

60 mmHg, prompted stepwise 1% reductions in desflurane concentration for Bispectral Index values that remained less than 70. Additional intravenous fluids were also given as deemed appropriate by the responsible anesthesiologist. Similarly, atropine or intermittent boluses of ephedrine were given as required to treat bradycardia or persistent hypotension.

Thirty minutes before the anticipated end of surgery, a 0.15-mg/kg bolus dose of morphine was given intravenously. After skin closure, desflurane and remifentanil were discontinued, and residual neuromuscular blockade was antagonized with 40–60 μg/kg intravenous neostigmine and 15–20 μg/kg intravenous atropine. The trachea was extubated when patients responded to the verbal commands, spontaneous respiratory rate exceeded 12 breaths/min, and end-tidal carbon dioxide partial pressure was less than 45 mmHg.

Patients were transferred to the postanesthesia care unit (PACU) within 5 min of tracheal extubation. They remained in the unit for at least 4 h and were given oxygen *via* a facemask at a rate of 5 l/min throughout this period. Postoperative pain was initially treated with morphine chlorohydrate, which was titrated as required by nurses who were unaware of patients' group assignments. Boluses of morphine (3 mg) were given at 5-min intervals until the behavioral pain score (defined in the Measurements section) was less than 1 or the verbal rating scale score for pain was less than 2. However, morphine administration was discontinued in patients when the sedation score (defined in the Measurements section) was greater than 2 or the respiratory rate was less than 12 breaths/min. Subsequently, within 4 h after tracheal extubation, patients were connected to a PCA device set to deliver 1 mg morphine as an intravenous bolus with a 5-min lockout interval; continuous infusion was not allowed. This PCA regimen was continued for 48 h after tracheal extubation.

*Measurements*

Baseline heart rate and systolic arterial pressure were defined as the mean of the two lowest measurements recorded during a 3- to 5-min interval immediately before induction of anesthesia. Values from all routine anesthetic monitors, including Bispectral Index monitoring (Aspect A-2000® EEG monitor; Aspect Medical Systems, Natick, MA), were recorded at 5-min intervals during surgery.

The total dose of remifentanil given in the operating room was recorded, as was the age-adjusted desflurane dose in MAC/h.[18] Complications including laryngospasm, bronchospasm, respiratory depression, muscular rigidity, agitation, and shivering were recorded. Pain was evaluated for the first 15 min after extubation with a behavioral score (0 = calm patient with no verbal or behavioral manifestation of pain, 1 = behavioral or verbal expression of pain, 2 = intense behavioral or verbal manifestation [crying or extreme agitation]). This behavioral pain scale was performed 5, 10, and 15 min after tracheal extubation.

Patients assessed pain intensity by giving both VAS and verbal rating scale scores at 15-min intervals during the first hour and then hourly for 3 h. Subsequently, pain was evaluated only with the VAS at 4-h intervals for an additional 44 h.

The pain threshold for mechanical static (punctuate) stimuli was assessed using calibrated von Frey hairs (0.057–178 g/mm$^2$). The patients were instructed to close their eyes during the procedure. Care was taken to avoid stroking the skin with the hair and to apply only a pressure stimulus. Filaments were applied to the designated point on the skin for approximately 1 s. Von Frey hair applications were separated by at least 30 s to reduce the likelihood of anticipatory responses. The von Frey filaments were applied in ascending order of stiffness. Tactile pain threshold was defined as the smallest force (g/mm$^2$) necessary to bend a von Frey hair, which was just perceived as painful. Three determinations with an interval of 30 s were made at each assessment, and a mean was calculated. If tactile pain threshold exceeded hair number 19 (178 g/mm$^2$), the sensitivity was censored at number 20.

A handheld electronic pressure algometer (Somedic AB, Stockholm, Sweden) with a 0.28-cm$^2$ probe area was used to determine pressure pain threshold. The patients were instructed to immediately activate a push button, which freezes the digital display, when pain was perceived. The average of three measurements with an interstimulus interval of 60 s was defined as pressure pain threshold value. Values were expressed in kPa.

Tactile and pressure pain thresholds were measured in an area 2–3 cm from the incision at three levels (top, middle, and bottom) and on the inner forearm. A mean value for the three periincisional regions was calculated and used for statistical comparisons.

The extent of mechanical static (punctuate) hyperalgesia to von Frey hair stimulation proximal to the surgical wound was assessed with von Frey hair No. 16 (pressure = 122 g/mm$^2$) according to the methods described by Ilkjaer *et al.*[22] Hyperalgesia was determined by stimulating along three linear paths at right angles to the top, middle, and bottom sides of the surgical incision in steps of 5 mm at 1-s intervals, starting well outside the hyperalgesic area. During the first test, the regions were marked. Stimulations continued toward the incision until patients reported a clear change in sensation (*e.g.*, burning, tenderness, or more intense pricking). The distance (in cm) from the incision to where sensations changed was measured, and a sum of the three assessments (top, middle, and button) was calculated and used for statistical comparisons.

Dynamic allodynia was investigated using a soft brush 2–3 cm from the incision. Allodynia was considered to

be present if stroking the skin evoked a clear sensation of pain. We repeated this test three times at 24 and 48 h after surgery. Peak flow (l/min) was determined the evening before surgery. Postoperative pain scores on a VAS scale during peak flow measurement were also assessed.

Anesthetic-related complications were recorded, including nausea, vomiting, pruritus, dysphoria, hallucinations, and diplopia. Nausea and vomiting were treated by intravenous bolus of 0.5 mg droperidol. Sedation was monitored using the following four-point rating scale: 0 = patient fully awake, 1 = patient somnolent and responsive to verbal commands, 2 = patient somnolent and responsive to tactile stimulation, 3 = patient asleep and responsive to painful stimulation. Postoperative respiratory depression was defined by the combination of a sedation score greater than 1 and a respiratory rate less than 10 breaths/min.

We assessed short-term memory and working memory using the Digit Span Backward Test (DSBT).[23] For this test, subjects were asked to repeat a string of digits in the original order (digit span forward, maximal score = 7) and in the reverse order (digit span backward, maximal score = 7). To measure cognitive and perceptual speed, patients were asked to take a Digit Symbol Substitution Test (DSST).[23] DSBT, DSST, and anxiety VAS were performed preoperatively the evening before surgery, and postoperatively at 24 and 48 h.

Patients were asked to complete a written questionnaire on the first and second postoperative days to evaluate psychopharmacologic effects that have been reported after ketamine; these included altered color perception, reduced visual acuity, changes in hearing, hallucinations, altered body image, feelings of unreality, anxiety, aggression, altered physical strength, dizziness, discomfort, illness, and nausea.[24]

Quantitative sensory tests were performed in each center by the same experienced investigator (V. J. or P. R.) preoperatively the evening before surgery and postoperatively at 24 and 48 h. The study ended after 48 h.

*Statistical Analysis*

The extent of hyperalgesia to von Frey hair stimulation proximal to the surgical wound was considered our primary endpoint. The secondary endpoints were other results of quantitative sensory tests, VAS pain scores, and morphine consumption. Our sample-size estimate was based on the expected differences in the extent of hyperalgesia to von Frey hair stimulation proximal to the surgical wound at 48 h between the large- and small-dose remifentanil groups. In a preliminary study of 20 patients, we observed that the extent of hyperalgesia for punctuate mechanical stimuli around a xiphopubic incision was 7 cm with a SD of 4 cm. A sample size estimate indicated that 21 patients/group would give a power of 80% at an $\alpha$ level of 0.05 for detecting a difference in 50% in the extent of hyperalgesia to von Frey hair stimulation proximal to the surgical wound. The study size was thus prospectively set to 75 patients (25 patients/group).

Age, weight, height, duration of procedures, temperature at end of the study, and cumulative postoperative morphine consumption at 48 h were compared with an unpaired Student *t* test. The relative frequencies of sex, American Society of Anesthesiologists physical status, ephedrine use, psychopharmacologic effects, nausea, and vomiting were compared with the Fisher exact test. Hemodynamic variables, Bispectral Index, pain thresholds, peak flow, and VAS scores for 48 h were analyzed with two-way analysis of variance for repeated measures. DSBT and DSST scores were analyzed with the nonparametric Kruskal-Wallis test. Statistical analysis was performed with Statview for Windows (version 5.0; SAS Institute Inc, Cary, NC). Results are presented as mean ± SD or median (interquartile range); $P < 0.05$ was considered statistically significant.

## Results

Seventy-five patients were enrolled in the study. One patient was excluded from the large-dose remifentanil–ketamine group because of respiratory depression that occurred postoperatively in the PACU and was treated with a 0.4-mg injection of naloxone. This patient arrived in the PACU with a VAS pain score of 100 mm. He received a morphine dose of 21 mg by intravenous titration, which corresponded to a total dose of 33 mg, including the intraoperative bolus of 0.15 mg/kg. Respiratory depression occurred 1 h after the last morphine injection. It was attributed to excessive perioperative morphine administration.

Morphometric and demographic characteristics, duration of surgery and anesthesia, and types of surgical procedures were comparable in the three treatment groups (table 1). Desflurane requirement was significantly greater in the small-dose remifentanil group than in the other two groups ($P < 0.05$; table 2). The times from the remifentanil discontinuation until awakening and tracheal extubation were comparable in the three groups (table 2).

Bispectral Index values were comparable in the large- and small-dose remifentanil groups but greater in the large-dose remifentanil–ketamine group ($P < 0.05$; table 3). Intraoperatively, systolic and diastolic pressures were similar in the three groups; however, heart rate was generally higher ($P < 0.05$; table 3) in the small-dose remifentanil group. More ephedrine was required in the large-dose remifentanil–ketamine group than in the two other groups to maintain hemodynamic stability ($P < 0.05$; table 2).

**Table 1. Morphometric and Demographic Data, Surgical Procedures, and Duration of Surgery and Anesthesia**

| | Small-dose Remifentanil (n = 25) | Large-dose Remifentanil (n = 25) | Large-dose Remifentanil–Ketamine (n = 24) |
|---|---|---|---|
| Age, yr | 58 ± 13 | 56 ± 12 | 59 ± 13 |
| Weight, kg | 67 ± 13 | 69 ± 12 | 67 ± 13 |
| Height, cm | 164 ± 10 | 168 ± 9 | 167 ± 7 |
| Sex, M/F | 10/15 | 9/16 | 9/16 |
| ASA status, I/II/III | 10/12/3 | 12/10/3 | 9/12/4 |
| Procedure, No. of patients | | | |
| Right colectomy | 5 | 3 | 5 |
| Colectomy with colorectal anastomosis | 11 | 15 | 12 |
| Colectomy with coloanal anastomosis | 7 | 6 | 7 |
| Total colectomy | 2 | 1 | 0 |
| Duration of anesthesia, h | 4.4 (3.3–5.7) | 4.3 (3.1–4.6) | 4.4 (3.3–5.0) |
| Duration of surgery, h | 3.5 (2.6–4.5) | 3.5 (2.5–3.8) | 3.5 (2.6–4.2) |

Values are presented as mean ± SD, median (interquartile range), or number of patients. There were no statistically significant differences among the groups.

Tactile pain thresholds adjacent to the incision were significantly less at 24 and 48 postoperative hours in the large-dose remifentanil group than in the other groups ($P < 0.01$; fig. 1). However, there were no significant differences among the groups for pressure pain threshold determined with the algometer at 2–3 cm from the incision (table 4). Moreover, no clear sensation of pain could be evoked in any patient by stroking the skin with a brush adjacent to the incision.

Extent of hyperalgesia to von Frey hair stimulation proximal to the surgical incision was easily detected in all patients and was significantly larger at 24 and 48 h in the large-dose remifentanil group than in the other two groups ($P < 0.03$; fig. 2).

Tactile and pressure pain thresholds measured on the forearm did not differ preoperatively *versus* postoperatively in any group (data not shown).

Visual analog scale (fig. 3) and verbal rating scale (data not shown) pain scores at rest and after peak flow (table 3) did not differ among the three groups. Peak flow values were also comparable (table 4).

Although the mean time to first morphine administration and the cumulative amount of intravenous morphine given by nurses in the PACU did not differ among the three groups (table 2), postoperative morphine consumption, including morphine titrated in the PACU, was significantly greater throughout the 48-h postoperative period in the large-dose remifentanil group than in the other groups ($P < 0.05$; table 2).

**Table 2. Anesthetic Characteristics, Postoperative Morphine Use, and Nausea and Vomiting**

| | Small-dose Remifentanil (n = 25) | Large-dose Remifentanil (n = 25) | Large-dose Remifentanil–Ketamine (n = 24) |
|---|---|---|---|
| Remifentanil dose, mg | 0.9 ± 0.3* | 6.7 ± 3.1 | 6.5 ± 3.4 |
| Desflurane, MAC/h | 0.8 ± 0.2* | 0.5 ± 0.2 | 0.6 ± 0.2 |
| Ephedrine, No. of doses/No. of patients | 9/17 | 10/13 | 50/15† |
| Final intraoperative temperature, °C | 36.6 ± 0.7 | 36.3 ± 0.8 | 36.3 ± 0.9 |
| Awakening time, min | 14 ± 6 | 13 ± 5 | 14 ± 6 |
| Extubation time, min | 16 ± 6 | 14 ± 6 | 15 ± 4 |
| Time to first postoperative morphine, min | 35 (28–46) | 24 (20–33) | 41 (32–52) |
| Morphine given in PACU, mg | 16 (10–24) | 20 (17–27) | 20 (14–23) |
| 0–48 h cumulative postoperative morphine consumption, mg | 68 (50–91) | 86 (59–109)‡ | 62 (48–87) |
| Postoperative nausea and vomiting, No. of patients | 7 | 8 | 8 |
| Droperidol, No. of doses/No. of patients | 8/7 | 8/8 | 8/8 |

Times (awakening, extubation, first morphine administration) were defined from remifentanil discontinuation. The cumulative postoperative morphine consumption excluded the dose of 0.15 mg/kg given 30 min before the end of surgery. Values are presented as mean ± SD, median (interquartile range), or number of patients.

* $P < 0.05$ *vs.* large-dose remifentanil and large-dose remifentanil–ketamine groups. † $P < 0.05$ *vs.* small-dose remifentanil and large-dose remifentanil groups. ‡ $P < 0.05$ *vs.* small-dose remifentanil and large-dose remifentanil–ketamine groups.

MAC = minimum alveolar concentration; PACU = postanesthesia care unit.

The incidences of nausea and vomiting and of droperidol consumption (table 2), the distribution of sedation and anxiety scores (data not shown), and the responses to the written questionnaire evaluating postoperative ketamine psychopharmacologic effects were similar in all groups. However, one patient in the large-dose remifentanil–ketamine group reported hallucinations at 24 and 48 h after surgery and altered body image at 24 h, and another patient in the same group reported altered color perception, dizziness, and reduced visual activity at 24 h. Eight patients in the small-dose remifentanil group, five in the large-dose remifentanil group, and six in the large-dose remifentanil–ketamine group declined to take the DSST postoperatively. All patients performed the DSBT at 24 and 48 h, however. No intergroup differences were found in the results of the DSBT or DSST. The DSBT score (mean scores between 12 and 17) was

**Table 3. Intraoperative Heart Rate, Mean Arterial Blood Pressure, and Bispectral Index of the Electroencephalogram**

| | Small-dose Remifentanil (n = 25) | | | Large-dose Remifentanil (n = 25) | | | Large-dose Remifentanil–Ketamine (n = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR, beats/min | MAP, mmHg | BIS | HR, beats/min | MAP, mmHg | BIS | HR, beats/min | MAP, mmHg | BIS |
| Before induction | 75 ± 13 | 72 ± 14 | 96 ± 4 | 73 ± 14 | 76 ± 14 | 97 ± 2 | 81 ± 18 | 76 ± 13 | 95 ± 5 |
| After induction | 74 ± 13 | 65 ± 15 | 59 ± 21† | 70 ± 12 | 70 ± 17 | 57 ± 22 | 78 ± 14 | 70 ± 10 | 48 ± 18 |
| OTI | 80 ± 16 | 83 ± 21 | 65 ± 15 | 74 ± 21 | 75 ± 20 | 67 ± 12 | 78 ± 16 | 76 ± 20 | 67 ± 16 |
| Incision | 69 ± 15*† | 67 ± 19 | 53 ± 14 | 59 ± 14 | 53 ± 12 | 50 ± 10‡ | 59 ± 7 | 50 ± 9 | 60 ± 12 |
| Piece | 74 ± 13† | 58 ± 13 | 43 ± 10† | 67 ± 9 | 57 ± 12 | 50 ± 12‡ | 68 ± 14 | 50 ± 12 | 57 ± 10 |
| Skin closure | 86 ± 18* | 63 ± 17 | 56 ± 15† | 67 ± 18 | 67 ± 18 | 64 ± 14 | 84 ± 20 | 69 ± 16 | 67 ± 14 |
| Extubation | 84 ± 11 | 78 ± 12 | 92 ± 3 | 89 ± 11 | 86 ± 13 | 96 ± 3‡ | 86 ± 16 | 90 ± 12 | 89 ± 9 |

Values are presented as mean ± SD.

* $P < 0.05$ *vs.* large-dose remifentanil group. † $P < 0.05$ *vs.* large-dose remifentanil–ketamine group. ‡ $P < 0.05$ *vs.* large-dose remifentanil–ketamine group.

BIS = Bispectral Index of the electroencephalogram; HR = heart rate; MAP = mean arterial blood pressure; OTI = orotracheal intubation.

not impaired postoperatively in any group; however, the mean DSST scores, which were between 41 and 47 preoperatively, were significantly decreased by 22–34% at 24 h after surgery and returned to baseline at 48 h in all three groups.

## Discussion

We confirmed our hypothesis that a relatively large dose of intraoperative remifentanil increases pain sensitivity as evidenced by a reduction of the postoperative tactile pain threshold proximal to the surgical wound and an extension of periincisional hyperalgesia in our large-dose remifentanil group. This phenomenon lasted throughout both postoperative days and was associated with an increase in morphine administered by PCA. We also found that giving a small dose of ketamine during and after surgery completely prevented the increase in postoperative pain sensitivity and punctuate hyperalgesia that otherwise resulted from large-dose remifentanil administration. Moreover, patients who received a large dose of remifentanil with ketamine had significantly less postoperative morphine requirements than those receiving the large dose of remifentanil only; in fact, the dose was comparable to that of the small-dose remifentanil patients.

The differences in postoperative morphine requirements between the small- and large-dose remifentanil groups were less marked than we observed in a previous study.[12] The reasons are likely related to differences in the design of these two studies. In the current study, we gave remifentanil a constant rate throughout the intraoperative period, whereas in the previous study, remifentanil was titrated to patient responses. Consequently, in the previous study,[12] the remifentanil infusion rate frequently exceeded our current limit of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This difference in the rate of infusion may account for the differences observed in postoperative morphine requirements in the large-dose remifentanil groups in the two

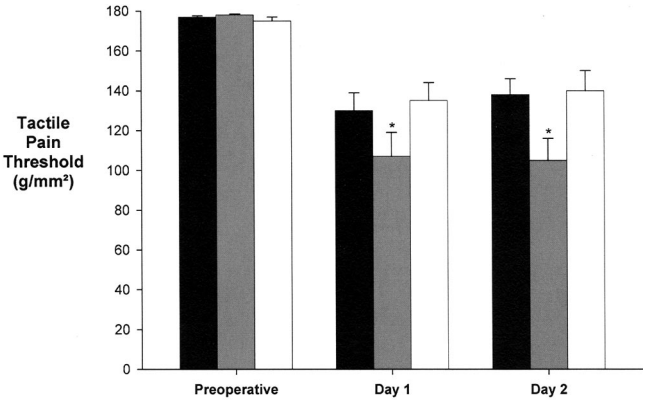


**Fig. 1. Tactile pain thresholds (g/mm²) determined with von Frey hair 2–3 cm proximal and perpendicular to the top, middle, and bottom of the surgical incision. *Solid bars* = small-dose remifentanil group; *gray bars* = large-dose remifentanil group; *open bars* = large-dose remifentanil–ketamine group. Results are expressed as mean ± SD. * Statistical difference from small-dose remifentanil and large-dose remifentanil–ketamine groups ($P < 0.01$).**

**Table 4. Peak Flow, VAS Pain Scores during Peak Flow, and Pressure Pain Threshold with Algometer Preoperatively and Postoperatively**

| | Small-dose Remifentanil (n = 25) | Large-dose Remifentanil (n = 25) | Large-dose Remifentanil–Ketamine (n = 24) |
|---|---|---|---|
| Preoperative | | | |
| Peak flow, l/min | 380 (280–450) | 360 (300–450) | 320 (275–400) |
| Algometer, kPa | 180 ± 73 | 177 ± 90 | 187 ± 79 |
| 24 h postoperative | | | |
| Peak flow, l/min | 100 (15–120) | 100 (70–150) | 100 (55–150) |
| VAS, mm | 42 ± 26 | 44 ± 21 | 36 ± 20 |
| Algometer, kPa | 66 ± 36 | 74 ± 50 | 60 ± 38 |
| 48 h postoperative | | | |
| Peak flow, l/min | 100 (95–155) | 120 (80–150) | 95 (60–150) |
| VAS, mm | 43 ± 20 | 37 ± 23 | 33 ± 18 |
| Algometer, kPa | 64 ± 41 | 72 ± 45 | 67 ± 45 |

Values presented as median (interquartile range) or means ± SDs. No significant difference was found among the groups.

VAS = visual analog scale.

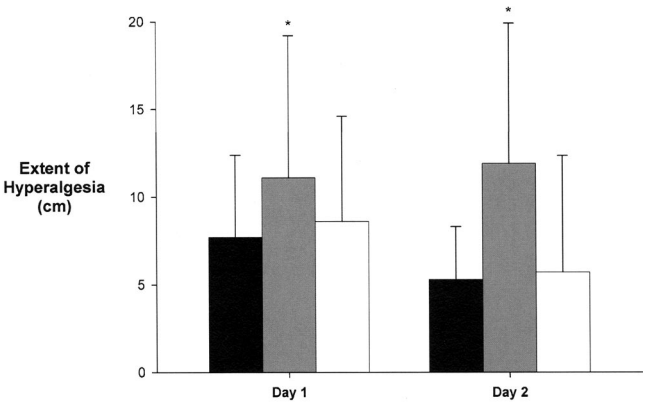


**Fig. 2. Extent of hyperalgesia to von Frey hair number 16 (pressure = 122 g/mm$^2$) stimulation proximal to the surgical wound (distance from wound in cm). *Solid bars* = small-dose remifentanil group; *gray bars* = large-dose remifentanil group; *open bars* = large-dose remifentanil–ketamine group. Results are expressed as mean ± SD. * Statistical difference ($P < 0.03$) from small-dose remifentanil and large-dose remifentanil–ketamine groups.**

studies because acute opiate tolerance seems to be dose dependent.[1,9,11,25]

Previous studies clearly demonstrated that there is an area of mechanical hyperalgesia around a surgical incision.[22,26–28] However, the current study is the first to evaluate to what extent intraoperative opioid use contributes to this hyperalgesia. Koppert *et al.*[9] reported that, in volunteers, the area of hyperalgesia surrounding a transcutaneous electrical stimulation at a high current density increased after discontinuation of remifentanil when administered at a rate of 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but not at a rate of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. It would also be reasonable to assume that periincisional hyperalgesia observed in the small-dose remifentanil group was mainly induced by surgery, whereas 0.40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil used in the large-dose remifentanil group triggered approximately half of the observed mechanical hyperalgesia.

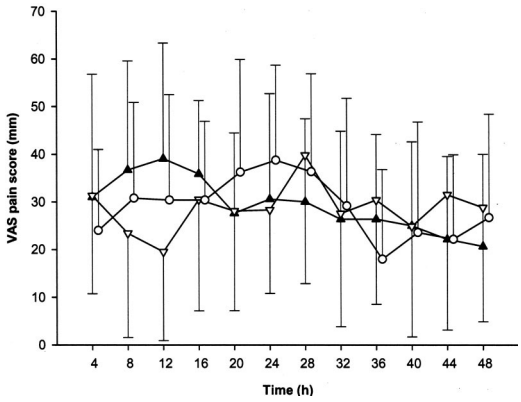


**Fig. 3. Visual analog pain scores (VAS) at rest during 48 postoperative hours. *Closed triangle* = small-dose remifentanil group; *open triangle* = large-dose remifentanil group; *open circle* = large-dose remifentanil–ketamine group. Results are expressed as mean ± SD. There were no statistically significant differences among the three groups.**

As in animal experiments,[25] it is possible to imagine that postoperative morphine potency was reduced in the large-dose remifentanil patients in whom allodynia proximal to the wound was most profound and extended, which accounts to greatest total postoperative PCA morphine consumption in these patients—possibly resulting from an acute tolerance to the analgesic effects of morphine.

In contrast to static mechanical allodynia triggered with von Frey filaments, we were unable to detect dynamic mechanical allodynia triggered by brushing as in experimental models of secondary mechanical hyperalgesia.[9] One reason may be that these two types of allodynia have dissimilar origins. Punctuate allodynia is elicited by input from high-threshold A-$\delta$ fibers,[29] whereas mechanical dynamic allodynia is elicited from low-threshold A-$\beta$ fibers.[30]

Despite the differences between the large-dose remifentanil group and the other groups in tactile pain threshold proximal to the surgical wound and in extent of hyperalgesia tested by von Frey hair filament, pressure pain thresholds tested by algometer and VAS pain scores at rest and during peak flow were comparable in the three groups. These results are difficult to explain; however, they support those of other studies using the same measurements.[26,28,31] One explanation would be that the potential increase in pain scores was counteracted by increased PCA morphine use. Moreover, the lack of differences in postoperative peak flow values between the groups in the current study may be due to the dependence of this measurement on pain after abdominal surgery.[32]

Although the clinical implication of the area of periincisional hyperalgesia remains poorly understood, hyperalgesia proximal to the wound was found to be present 3 months after surgery in patients recovering from abdominal hysterectomy,[22] and long-term incisional pain at 1 month, 6 months, and 1 yr after open colorectal surgery was more frequent in patients who experienced the most extended hyperalgesia surrounding the surgical wound during the initial 72 postoperative hours.[28] Therefore, our results suggest that relatively large doses of intraoperative remifentanil without concomitant small-dose ketamine might be deleterious in patients at risk for chronic postoperative pain such as those undergoing thoracotomy and amputation.[33] Further studies are necessary though to confirm whether the extension of periincisional hyperalgesia may be considered a prognostic factor of chronic postsurgical pain.

Many mechanisms may explain remifentanil-induced hyperalgesia observed in the current study;[15] these include extensive internalization and thereby inactivation of $\mu$-opioid receptors by remifentanil,[34] opioid-induced up-regulation of the cyclic adenosine monophosphate pathway,[35] spinal dynorphin release,[3,36] and activation of central NMDA nociceptive systems.[15,25] That the

NMDA receptor antagonist ketamine was able to prevent the increase in postoperative hyperalgesia triggered by a large dose of remifentanil is consistent with the hypothesis that pronociceptive processes involving NMDA receptor activation account for opioid-induced hyperalgesia and acute opioid tolerance. In accord with this hypothesis, it was recently reported that remifentanil stimulates different NMDA receptor subunit combinations (NR1A/2A, NR1A/2B).[37] The ability of ketamine to reduce both hyperalgesia and postoperative morphine consumption supports the possibility that the effect of ketamine on opioid-induced hyperalgesia results in the reduction of opioid consumption.[2,25,33]

Few side effects were noted in the large-dose remifentanil–ketamine group. The case of severe respiratory depression requiring naloxone was likely caused by the large dose of morphine that was administered perioperatively (33 mg), as we have previously observed.[38] Effectively, according to studies evaluating respiratory interactions between opioids and ketamine,[39,40] it seems unlikely that this case of respiratory depression was related to ketamine. Two patients in the large-dose remifentanil–ketamine group had ketamine-induced central nervous system side effects at the specific written questionnaire, albeit without significant differences in patient responses among the three groups. However, we did not detect any effect of small dose ketamine on DSBT or DSST. The results of the current study seem consistent with a quantitative systematic reviews in which small-dose ketamine ($< 2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) given postoperatively did not specifically increase the incidence of hallucinations or impair cognitive functioning.[33,41–43]

Because the patients in the small-dose remifentanil group received larger doses of desflurane, an alternative explanation for our findings would be that the larger doses of desflurane prevented surgery-induced hyperalgesia, compared with the smaller doses received by the patients in the large-dose remifentanil group. Indeed, halogenated anesthetics have been shown to decrease hyperexcitability of spinal dorsal horn neurons after tissue injury.[44] Volatile anesthetics, including desflurane, seem to block NMDA receptors.[45] However, volatile anesthetics do not prevent subsequent hyperexcitability of spinal dorsal horn neurons even though they suppress evoked responses to incision.[44] Furthermore, response of NMDA receptors expressed in oocytes to glutamate are suppressed only 20% at 0.5 MAC and 40% at 1.0 MAC desflurane. This suggests that the small 0.3% difference in desflurane concentration does not account for the exaggerated hyperalgesia in the large-dose remifentanil group.

In summary, intraoperative administration of a relatively large dose of remifentanil increased postoperative pain sensitivity, specifically periincisional hyperalgesia. A small dose of ketamine prevented hyperalgesia, implicating NMDA receptors in remifentanil-induced hyperalgesia and confirmed the benefits of administering small-dose ketamine when relatively large intraoperative remifentanil doses are required.

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