Anesthesiology 2006; 105:111–9 

# *Low-dose Intravenous Ketamine Potentiates Epidural Analgesia after Thoracotomy*

*Manzo Suzuki, M.D.,* Syuji Haraguti, M.D.,† Kikuzo Sugimoto, M.D., Ph.D.,‡ Takehiko Kikutani, M.D.,* Yoichi Shimada, M.D., Ph.D.,§ Atsuhiro Sakamoto, M.D., Ph.D.‖*

***Background:*** **Ketamine potentiates intravenous or epidural morphine analgesia. The authors hypothesized that very-low-dose ketamine infusion reduces acute and long-term postthoracotomy pain.**

***Methods:*** **Forty-nine patients scheduled to undergo open thoracotomy were randomly assigned to receive one of two anesthesia regimens: continuous epidural infusion of ropivacaine and morphine, along with intravenous infusion of ketamine (0.05 mg · kg$^{-1}$ · h$^{-1}$ [approximately 3 mg/h], ketamine group, n = 24) or placebo (saline, control group, n = 25). Epidural analgesia was continued for 2 days after surgery, and infusion of ketamine or placebo was continued for 3 days. Pain was assessed at 6, 12, 24, and 48 h after surgery. Patients were asked about their pain, abnormal sensation on the wound, and inconvenience in daily life at 7 days and 1, 3, and 6 months after surgery.**

***Results:*** **The visual analog scale scores for pain at rest and on coughing 24 and 48 h after thoracotomy were lower in the ketamine group than in the control group (pain at rest, 9 ± 11 *vs.* 25 ± 20 and 9 ± 11 *vs.* 18 ± 13; pain on coughing, 26 ± 16 *vs.* 50 ± 17 and 30 ± 18 *vs.* 43 ± 18, mean ± SD; $P = 0.002$ and $P = 0.01$, $P < 0.0001$ and $P = 0.02$, respectively). The numerical rating scale scores for baseline pain 1 and 3 months after thoracotomy were significantly lower in the ketamine group (0.5 [0–4] *vs.* 2 [0–5] and 0 [0–5] *vs.* 1.5 [0–6], median [range], respectively; $P = 0.02$). Three months after surgery, a higher number of control patients were taking pain medication (2 *vs.* 9; $P = 0.03$).**

***Conclusions:*** **Very-low-dose ketamine (0.05 mg · kg$^{-1}$ · h$^{-1}$) potentiated morphine–ropivacaine analgesia and reduced postthoracotomy pain.**

THORACIC surgery is one of the most painful surgeries. Intercostal nerve damage during surgery induces severe postoperative pain, which may be related to the development of long-term pain after the thoracotomy.[1] Katz *et al.*[2] demonstrated that aggressive postoperative pain relief contributes to a reduction in long-term postoperative pain. Compared with patients who received opioid intravenously for postoperative analgesia, patients who received epidural coadministration of opioid and a local anesthetic had a lower incidence of long-term postthoracotomy pain.[3] Administration of an opioid during or after surgery leads to opioid tolerance and hyperalgesia, which are both mediated by *N*-methyl-D-aspartate receptor activation.[4] A bolus or continuous administration of ketamine during surgery, especially when coadministered with an opioid, provides excellent postoperative analgesia, suggesting that ketamine either prevents acute opioid tolerance or potentiates opioid analgesia.[5,6] A study in rats suggested that administration of ketamine prevents the development of fentanyl-induced hyperalgesia.[7] Therefore, we hypothesized that continuous intravenous ketamine infusion at a very low dose of 0.05 mg · kg$^{-1}$ · h$^{-1}$, which was expected to produce a plasma ketamine concentration of 20 ng/ml, would potentiate epidural morphine and ropivacaine-induced analgesia after standard open thoracotomy and improve long-term postoperative pain.

To test this hypothesis, we administered a low dose of ketamine or placebo to patients who received an epidural infusion of morphine and ropivacaine for postthoracotomy pain. We then examined the pain status of the patients between 6 and 48 h; at 1 week; and at 1, 3, and 6 months after the completion of thoracotomy. We studied patients who underwent standard open thoracotomy and did not develop recurrence or metastasis up to 6 months after surgery.

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

## Materials and Methods

### *Patient Selection*

The institutional review board of the Second Hospital Nippon Medical School (Kanagawa, Japan) approved this study, and each patient gave written informed consent. We enrolled 50 patients who were scheduled to undergo open thoracotomy in this double-blind, placebo-controlled, randomized, two-group parallel study. The length of incision was approximately 15 cm. Surgical manipulation had to include cutting a rib and reconstructing it using a rib reconstruction pin, and cutting and reconstruction of one or more muscles such as the latissimus dorsi muscle. Exclusion criteria were morbid obesity (body mass index ≥ 30 kg/m$^2$); allergy to local anesthetics, opioids, or ketamine; diabetes; psychiatric disorder; and age over 80 yr. Patients were assigned to

* Instructor, § Associate Professor, Department of Anesthesiology, † Assistant Professor, Department of Surgery, Second Hospital Nippon Medical School, Kanagawa, Japan. ‡ Assistant Professor, Department of Anesthesiology, Second Hospital Nippon Medical School. Current position: Chief in Anesthesiology, Higashitotuka Memorial Hospital, Kanagawa, Japan. ‖ Professor and Chair, Department of Anesthesiology, Nippon Medical School.

Received from the Department of Anesthesiology, Second Hospital, Nippon Medical School, Kanagawa, Japan. Submitted for publication October 24, 2005. Accepted for publication March 24, 2006. Supported by Hisamitsu Pharmaceutical Company, Tokyo, Japan.

Address correspondence to Dr. Suzuki: Department of Anesthesiology, Second Hospital Nippon Medical School, Kanagawa, Japan, 211-8533. manzo@nms.ac.jp. 

one of two groups using a computer-generated randomization schedule: the ketamine group, which received an epidural infusion of morphine and ropivacaine and intravenous infusion of ketamine, and the control group, which received epidural infusion of morphine and ropivacaine and intravenous infusion of placebo.

*Anesthesia and Postoperative Pain Control*

Premedication consisted of intramuscular injection of 0.5 mg atropine sulfate and 25 mg hydroxyzine 30 min before induction of anesthesia. In the operating room, the left or right antecubital vein was secured for perioperative infusion. An epidural catheter was placed in the right decubitus position *via* the thoracic 5–6 or 6–7 interspace. Ropivacaine, 0.75%, 6–8 ml, was injected through the epidural catheter. After sensory blockade to cold in the T4 dermatome was confirmed, 1.5 mg/kg propofol was administered intravenously to induce anesthesia, and 0.15 mg/kg vecuronium was administered intravenously to facilitate tracheal intubation. A double-lumen endobronchial tube was placed to perform differential one-lung ventilation. The right or left radial artery was secured for arterial pressure monitoring and arterial blood sampling. Monitoring included electrocardiography, blood hemoglobin oxygen saturation, end-tidal carbon dioxide tension, and noninvasive and invasive arterial pressure monitoring.

We previously determined the plasma concentration of ketamine that potentiates epidural morphine and bupivacaine analgesia for postthoracotomy pain.[8] We found that a plasma concentration of ketamine of 20 ng/ml or above reduced the visual analog scale (VAS) score at rest by approximately 50% compared with that in the control patients, who were given a placebo. After tracheal intubation, an intravenous infusion of 0.05 mg $\cdot$ $kg^{-1} \cdot h^{-1}$ ketamine or placebo at the same volume was started. The infusion rate of ketamine was determined by simulation in a target-controlled infusion program# to maintain a blood concentration of 20 ng/ml. The study drug, ketamine or placebo, was prepared and placed in the infusion pump by an investigator who did not participate in the administration of anesthesia or the evaluation of postoperative pain. General anesthesia was maintained with 0.5–1.0% isoflurane and a mixture of 50–60% oxygen with nitrous oxide.

Ropivacaine, 0.75%, 6–8 ml, was administered approximately every 90 min during surgery. At the end of skin closure, 2.5 mg morphine sulfate and 0.375% ropivacaine in a total volume of 5 ml were administered epidurally, followed by epidural infusion of ropivacaine and morphine as described below. After reversal of muscle relaxants by administration of 1.0 mg atropine sulfate and 2.0 mg neostigmine and after the patient regained consciousness, the trachea was extubated. The day of surgery was set as postoperative day 0.

*Postoperative Pain Management*

After surgery, all patients received a continuous epidural infusion of 0.05 mg/ml morphine and 0.15% ropivacaine at an initial rate of 3 ml/h or by an infusion pump (Coopdech CSP-100; Daiken-ika, Osaka, Japan). The rate of epidural infusion was adjusted according to the pain score. If a patient described the level of pain at rest to be 0 mm on a 100-mm VAS pain scale, the rate of infusion was decreased from 3 ml/h to 2 ml/h. If a patient described the pain score at rest to be more than 50 mm, the infusion rate was increased from 3 ml/h to 5 ml/h. Epidural infusion was continued for 48 h. All patients continued to receive infusion of ketamine or placebo for 72 h after surgery. Vital signs were checked once every hour up to 24 h after surgery, and then once every 4 h between 24 and 48 h after surgery. If the patient requested additional analgesia within 24 h of surgery, 50 mg intravenous flurbiprofen was administered. If the patient requested additional analgesia between 24 and 48 h after surgery, 60 mg loxoprofen (nonsteroidal antiinflammatory drug) was administered orally.

*Postoperative Rehabilitation Schedule*

After surgery, patients were instructed to lie quietly in bed until the next morning; then, they were instructed to sit up. A chest drainage tube was left in place until the air leakage stopped and the volume of pleural discharge decreased; however, the tube was kept in place for at least 48 h after surgery so that removal of the drainage tube did not affect the pain score. The date of removal of the chest drainage tube was recorded. The urinary catheter was removed on either the first or the second postoperative day. The patient was instructed to begin eating foods and walking at noon or in the evening of the first postoperative day. Patients who could not sit up until the evening of the first postoperative day or who could not walk on the second postoperative day were withdrawn from the study.

*Assessment of Pain in the Presence of Epidural Pain Control*

At 6, 12, 24, and 48 h after surgery (during epidural infusion), pain at rest, pain on coughing, nausea, pruritus, and somnolence were assessed using a 100-mm VAS with 0 mm indicating "no feeling" and 100 mm indicating "worst possible feeling." At each time, after the assessment of pain by the patient, the score was confirmed by testing whether the patient had sensory block to pinprick at the dermatome level of the bandage that covered the skin incision. Patients who did not have sensory block to pinprick were withdrawn from the study.

# STANPUMP program. Available at: http://anesthesia.lstanford.edu/pkpd. Accessed March 10, 2006.

*Pain Treatment and Pain Assessment after Cessation of Epidural Pain Control during Hospital Admission*

Starting on postoperative day 3, patients who requested oral pain medication for basal pain treatment were given oral loxoprofen three times a day. If the patient had severe pain, they were given 25 mg diclofenac as a rescue analgesic. The number of times the rescue analgesic was administered was recorded. On day 3, before the termination of ketamine infusion, patients were asked to rate their pain on an 11-point numerical rating scale (NRS), in which 0 = no pain and 10 = worst possible pain. On day 7, patients scored their usual (baseline) pain and worst pain on the NRS while performing particular activities. Also on day 7, the patients in the surgical ward were asked the following questions about unpleasant sensations on the surgical wound and whether they felt inconvenienced by the wound: (1) Do you feel an unpleasant sensation at the site of surgery? (yes/no) (2) If yes, how would you describe the sensation (*i.e.*, tingling, burning, heavy feeling, *etc.*)? (3) Do you feel inconvenienced by the surgical wound? (yes/no) (4) If yes, when do you feel inconvenienced by the surgical wound or wound-induced pain?

*Pain Assessment after Discharge from the Hospital*

When the patients were discharged from the hospital, they were given pain medication (tablets). The patients were instructed to take the pain tablets as needed, up to three tablets a day. At 1, 3, and 6 months after surgery, one of the investigators, who did not know the group assignment, called each patient's home and administered the same questionnaire that had been given on day 7.

*Statistical Analysis*

The primary endpoint of the study was the number of patients who felt baseline pain at 3 months after thoracotomy. Before performing the current study, we had performed a pilot study, including 16 patients who were scheduled to undergo thoracotomy, in which 8 patients received ketamine and 8 patients received placebo in a similar protocol as the current study, and the patients were observed for 3 months. At 3 months after surgery, 3 of the 8 patients who received ketamine and 6 of the 8 patients who received placebo had baseline pain (*i.e.*, NRS score $\geq 1$). When we calculated the required sample size for $\alpha = 0.05$ and $\beta = 0.2$, we found that 22 patients in each group were required to detect a significant difference. To increase the power of this study, we enrolled 25 patients in each group.

We used repeated-measures analysis of variance to compare VAS scores for pain at rest, pain on coughing, pruritus, nausea, and drowsiness at 6, 12, 24, and 48 h after surgery. The Fisher protected least squares difference was used for *post hoc* analysis. The Mann–Whitney U test was used to assess the significance of differences in the NRS score on day 3 and the NRS score for usual pain and worst pain on day 7 and at 1, 3, and 6 months after thoracotomy, between the ketamine and control groups. The total volumes of morphine and ropivacaine that were infused epidurally in the ketamine and control groups were compared using multivariate analysis of variance. The chi-square test was used to assess the significance of the differences between the ketamine and control groups in the number of patients who required rescue analgesics within 24 h and from 24 to 48 h after surgery; the number of patients who were taking pain medication on day 7; the number of patients who required rescue analgesics on days 3, 4, 5, 6, and 7; the number of patients who felt usual pain at 1, 3, and 6 months after surgery; the number of patients who were taking pain medication 1, 3, and 6 months after surgery; the number of patients who felt an unpleasant sensation on the surgical wound; and the number of patients who felt inconvenienced by the wound. Significance was set at the 95% level ($P < 0.05$).

## Results

*During Epidural Infusion of Morphine and Ropivacaine*

Fifty patients who were scheduled to undergo thoracotomy were enrolled in this study. The patients were diagnosed with lung carcinoma (n = 47), bronchiectasia (n = 2), and atypical mycobacteria infection (n = 1).

During epidural infusion of morphine and ropivacaine, one patient in the ketamine group reported nausea at 6 h after surgery, and the patient wanted to discontinue epidural morphine. This patient was withdrawn from the study. No patient had to be withdrawn from the study because of inability to sit up until the evening of the first postoperative day, inability to walk on the second postoperative day, or lack of sensory block to pinprick up to 48 h after surgery. Consequently, 49 patients were studied. These patients did not have any postoperative complications that delayed the rehabilitation schedule, and all patients received sufficient sensory block from the epidural analgesia. The patient characteristics and surgical data of the ketamine and control groups were similar (table 1). Epidural infusion of morphine and ropivacaine was temporarily suspended because of hypotension in 8 patients in this study (n = 3, suspended for 10 [7–12] h in the ketamine group; n = 5, suspended for 5 [3–10] h in the control group, median [range]). The VAS pain score during the period in which epidural infusion was temporarily suspended in these patients was nearly 0 mm, and data from these patients were included in the study. The volume of morphine and ropivacaine that was infused epidurally after surgery was similar in the two groups (table 2).

The VAS pain scores at rest and on coughing at 6, 12, 24, and 48 h after surgery were low in both groups.

**Table 1. Patient Characteristics**

| | Ketamine (n = 24) | Control (n = 25) |
|---|---|---|
| Age, yr | 66 ± 14 | 66 ± 9 |
| Sex, M:F | 14:10 | 15:10 |
| Height, cm | 158 ± 10 | 159 ± 7 |
| Weight, kg | 57 ± 12 | 55 ± 10 |
| Duration of anesthesia, min | 293 ± 61 | 311 ± 45 |
| Intraoperative ropivacaine, mg | 90 ± 30 | 94 ± 22 |
| Duration of chest drainage, days | 4 (2–12) | 3 (2–11) |

Data are shown as mean ± SD or median (range). None of the variables differed significantly between the two groups.

According to multivariate analysis, the VAS score for pain at rest was impacted by the drug ($P = 0.001$) and time ($P < 0.0001$), but not by the interaction of drug and time ($P = 0.05$). Twenty-four hours and 48 h after surgery, the VAS score for pain at rest was significantly less in the ketamine group than in the control group ($P = 0.002$ and $P = 0.01$; fig. 1A). According to multivariate analysis, the VAS score for pain on coughing was significantly influenced by the drug ($P = 0.006$), time ($P < 0.0001$), and the interaction of time and drug ($P = 0.0001$). The VAS score for pain on coughing was significantly less in the ketamine group than in the control group at 24 and 48 h after surgery ($P < 0.001$ and $P = 0.02$, 24 and 48 h after surgery, respectively; fig. 1B). Significantly fewer patients required rescue analgesics from 24 to 48 h after surgery in the ketamine group than in the control group (table 3).

According to the multivariate analysis, VAS scores for pruritus were not impacted by the drug ($P = 0.8$), time ($P = 0.3$), or the interaction of drug and time ($P = 0.7$). The VAS scores for pruritus were similar in the two groups at all measurement times during the 48-h observation period (table 2).

Drowsiness decreased over time ($P < 0.0001$) and was not affected by drug ($P = 0.4$) or the interaction between drug and time ($P = 0.7$). The VAS scores for drowsiness in the ketamine and control groups were similar at all times (table 2).

The VAS score for nausea was not impacted by drug ($P = 0.6$), time ($P = 0.7$), or the interaction of drug and time ($P > 0.9$) according to multivariate analysis. The VAS scores for nausea were similar in the ketamine and control groups at all measured times (table 2).

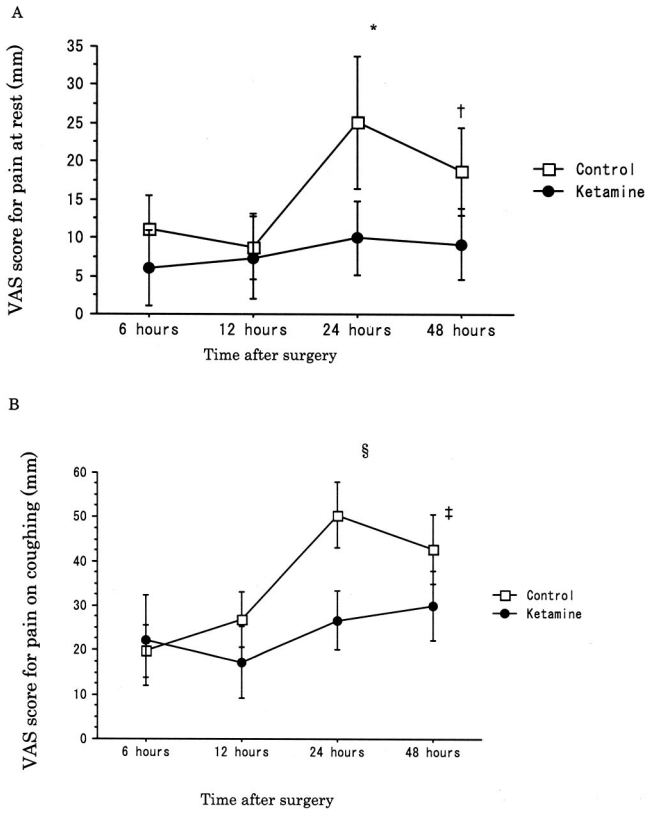


**Fig. 1. Visual analog scale (VAS) scores for pain at rest (*A*) and pain on coughing (*B*) during the first 48 h after thoracotomy in the ketamine and control groups. On the VAS, 0 mm = no pain and 100 mm = worst possible pain. * $P = 0.002$ *versus* control group. † $P = 0.01$ *versus* control group. ‡ $P < 0.0001$ *versus* control group. § $P = 0.02$ *versus* control group.**

**Table 2. Volume of Epidural Analgesic and VAS Scores at Various Times after Thoracotomy**

| | Ketamine (n = 24) | Control (n = 25) |
|---|---|---|
| Volume of morphine and ropivacaine, ml | | |
| 0–6 h | 18 ± 5 | 16 ± 7 |
| 6–12 h | 17 ± 6 | 17 ± 6 |
| 12–24 h | 35 ± 11 | 37 ± 12 |
| 24–48 h | 68 ± 22 | 79 ± 23 |
| Pruritus (VAS score), mm | | |
| 6 | 8 ± 17 | 11 ± 22 |
| 12 | 9 ± 14 | 12 ± 21 |
| 24 | 11 ± 24 | 13 ± 21 |
| 48 | 16 ± 20 | 13 ± 21 |
| Drowsiness (VAS score), mm | | |
| 6 | 49 ± 29 | 53 ± 24 |
| 12 | 49 ± 23 | 54 ± 21 |
| 24 | 22 ± 23 | 32 ± 29 |
| 48 | 22 ± 19 | 22 ± 25 |
| Nausea (VAS score), mm | | |
| 6 | 1.5 ± 6.0 | 0.0 ± 4.0 |
| 12 | 1.3 ± 6.0 | 0.8 ± 4.0 |
| 24 | 4.0 ± 17.0 | 3.0 ± 14.0 |
| 48 | 2.0 ± 12.0 | 1.0 ± 6.0 |

VAS = 100-mm visual analog scale, where 0 mm = no sensation and 100 mm = worst imaginable sensation. Data are presented as mean ± SD. There were no significant differences in the volume of epidural analgesic or any of the VAS scores.

**Table 3. Number of Patients Who Required Rescue Analgesics after Thoracotomy**

| | Ketamine (n = 24) | Control (n = 25) | *P* Value |
|---|---|---|---|
| 0–24 h | 7 | 7 | 0.9 |
| 24–48 h | 6 | 15 | 0.013 |
| Day 3 | 2 | 4 | 0.6 |
| Day 4 | 3 | 5 | 0.7 |
| Day 5 | 3 | 8 | 0.2 |
| Day 6 | 4 | 8 | 0.3 |
| Day 7 | 3 | 10 | 0.05 |

**Table 4. Numbers of Patients Who Received Pain Medication or Who Had an NRS Score of at Least 1 after Thoracotomy**

| | Day 7 | | 1 Month | | 3 Months | | 6 Months | |
|---|---|---|---|---|---|---|---|---|
| | Ketamine (n = 24) | Control (n = 25) | Ketamine (n = 24) | Control (n = 24) | Ketamine (n = 22) | Control (n = 22) | Ketamine (n = 22) | Control (n = 22) |
| Number of patients who received pain medication | 16 | 23 | 8 | 11 | 2 | 9 | 4 | 5 |
| *P* value | 0.06 | | 0.3 | | 0.03 | | > 0.9 | |
| Number of patients with NRS score ≥ 1 | 15 | 20 | 12 | 19 | 7 | 14 | 6 | 11 |
| *P* value | 0.2 | | 0.07 | | 0.03 | | 0.12 | |

NRS = numerical rating scale, where 0 = no pain and 10 = worst possible pain.

*After Cessation of Epidural Infusion*

Epidural analgesia was terminated 48 h after surgery, and ketamine infusion was terminated 72 h after surgery. On day 3, the NRS scores just before termination of ketamine infusion were comparable between the two groups (1 [0–5] *vs.* 0 [0–5], ketamine *vs.* control group, median [range]; $P = 0.3$). Sixteen patients in the ketamine group and 23 patients in the control group requested loxoprofen, three times a day, for pain on day 7 ($P = 0.06$; table 4). The numbers of patients requiring rescue analgesics between days 3 and 7 were comparable in the two groups (table 3). In one patient in the control group, loxoprofen did not provide sufficient pain relief at 1 month after surgery; therefore, paroxetine (selective serotonin reuptake inhibitor) was given to this patient. The data from this patient were included in the data analyses.

The NRS scores for average pain and worst pain on day 7 were significantly lower in the ketamine group than in the control group (1 [0–4] *vs.* 3 [0–8] and 2 [0–7] *vs.* 1 [0–9]; $P = 0.0008$ and $P = 002$, average and worst pain, respectively). Three weeks after surgery, 1 patient in the control group died of pneumonia. Between 1 and 3 months after surgery, 2 patients in the ketamine group had recurrence of lung carcinoma, and 2 patients in the control group developed cerebral metastasis; these patients were withdrawn from the study. Consequently, 48 patients (n = 24 in each group) were analyzed at 1 month after surgery, and 44 patients (n = 22 in each group) were analyzed at 3 and 6 months after surgery. The NRS score for usual pain was significantly lower in the ketamine group than in the control group at 1 and 3 months after surgery (fig. 2A). However, there was no significant difference in the NRS score for usual pain at 6 months after surgery between the two groups (fig. 2A). The NRS scores for worst pain at 1, 3, and 6 months after surgery were similar in the two groups (fig. 2B).

Significantly fewer patients reported usual pain (*i.e.*, NRS score ≥ 1) in the ketamine group than in the control group at 3 months but not at 7 days, 1 month, or 6 months after surgery (table 4). At 3 months but not at 1 week, 1 month, or 6 months after surgery, significantly fewer patients in the ketamine group were taking pain medication (table 4).

During the observation period (6 months after surgery), approximately 80% of the patients in both groups reported experiencing an unpleasant sensation on the surgical wound (no significant difference between groups; table 5). On day 7 and at 1 month after surgery, a significantly greater number of patients in the control group felt inconvenienced by the surgical wound; however, at 3 and 6 months after surgery, the numbers of

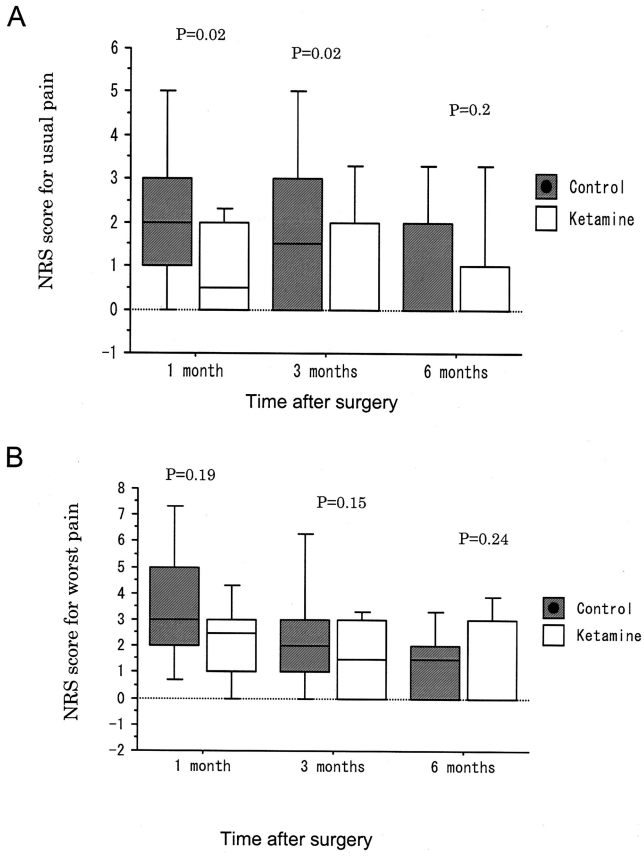


**Fig. 2. Changes in the numerical rating scale (NRS) scores for usual pain (*A*) and worst pain (*B*) in the ketamine (KM) and control (M) groups up to 6 months after surgery. The NRS is an 11-point scale where 0 = no pain and 10 = worst possible pain. *Horizontal bars* indicate the 10th, 25th, 50th, 75th, and 90th percentiles of the patients.**

**Table 5. Number of Patients Who Felt Various Types of Sensations on the Surgical Wound**

| Postoperative day 7 (n total) | Ketamine (n = 24) | Control (n = 25) | *P* Value |
|---|---|---|---|
| Total | 19 | 20 | 0.63 |
| Burning | 6 | 1 | |
| Tingling | 1 | 3 | |
| Heavy | 11 | 13 | |
| Itchy | 1 | 0 | |
| Sharp | 0 | 3 | |
| 1 Month after surgery (n total) | Ketamine (n = 24) | Control (n = 24) | *P* Value |
| Total | 20 | 21 | 0.9 |
| Burning | 2 | 0 | |
| Tingling | 8 | 9 | |
| Heavy | 8 | 7 | |
| Itchy | 1 | 0 | |
| Sharp | 1 | 5 | |
| 3 Months after surgery (n total) | Ketamine (n = 22) | Control (n = 22) | *P* Value |
| Total | 14 | 18 | 0.56 |
| Heavy | 6 | 9 | |
| Tingling | 8 | 8 | |
| Sharp | 0 | 1 | |
| 6 Months after surgery (n total) | Ketamine (n = 22) | Control (n = 22) | *P* Value |
| Total | 12 | 17 | 0.4 |
| Heavy | 7 | 8 | |
| Tingling | 5 | 6 | |
| Sharp | 0 | 3 | |

patients who felt inconvenienced were comparable in the two groups (table 6).

## Discussion

We found that patients who received a very low dose of ketamine, 0.05 mg · $kg^{-1}$ · $h^{-1}$, for 3 days after thoracotomy as an adjunct to epidural morphine–ropivacaine analgesia had lower pain scores at 48 h, 1 week, 1 month, and 3 months after surgery and that fewer patients in the ketamine-treated group were taking pain medication 3 months after surgery. Fewer patients in the ketamine group reported usual pain at 3 months after surgery.

*Pain Reduction Soon after Surgery*

Whether postoperative ketamine infusion reduces spontaneous pain soon after surgery remains controversial. Javery *et al.*[9] reported that after microdiscectomy, patients who received coadministration of ketamine and morphine using intravenous patient-controlled analgesia had reduced pain scores and morphine consumption compared with patients who received morphine alone. In contrast, after renal surgery, ketamine did not have an additive effect with epidural bupivacaine or epidural morphine analgesia.[10] In the current study, at 6 and 12 h after surgery, the VAS scores for pain at rest and pain on coughing in the ketamine and control groups did not significantly differ, perhaps because of a lingering effect of the epidural morphine and ropivacaine injected during and at the end of surgery. However, by the next day (first postoperative day), the effect of the intraoperative dose of epidural morphine and ropivacaine may have dissipated, and consequently, the patients receiving ketamine had significantly lower VAS scores for pain. The dose of ketamine in the current study was nearly identical to that administered in a previous study *via* patient-controlled analgesia after a mixture of morphine and ketamine was infused after microdiscectomy.[9] The level of acute postthoracotomy pain induced by rib fracture, local tissue trauma and damage to intercostal nerves is much higher than that induced by microdiscectomy. However, because of aggressive pain management with epidural coadministration of morphine and ropivacaine, the pain scores in the ketamine and control groups were low, and the dose of morphine was relatively small. In contrast, in previous studies that reported that the addition of ketamine to morphine analgesia after major surgery had no significant effect, a much higher dose of morphine was administered intravenously to manage a much higher score of pain.[10,11] An animal study on dextromethorphan, another *N*-methyl-D-aspartate receptor antagonist, showed that the ratio of the dose of opioid to that of dextromethorphan was important in preventing opioid-induced hyperalgesia.[12] A clinical study demonstrated that when coadministering ketamine and morphine *via* a patient-controlled analgesia pump, the ratio of the dose of ketamine to that of morphine was important.[13] In the current study, because the dose of epidural morphine was relatively small and stable and because nonopioid rescue analgesics were used, the need for ketamine to potentiate epidural morphine–induced analgesia might have been small. Ketamine at a very low dose may have sufficiently potentiated epidural morphine-and-ropivacaine–induced analgesia in the protocol used in this study.

**Table 6. Kinds of Inconvenience Felt by the Patients after Thoracotomy**

| Postoperative day 7 (n total) | Ketamine (n = 24) | Control (n = 25) | *P* Value |
|---|---|---|---|
| Total | 9 | 19 | 0.01 |
| I cannot make a large cough | 1 | 2 | |
| I cannot sit up smoothly | 6 | 12 | |
| I cannot sleep well | 1 | 4 | |
| I cannot move my shoulder | 1 | 0 | |
| I cannot take a deep breath | 0 | 1 | |
| None | 15 | 6 | |
| 1 Month after surgery (n total) | Ketamine (n = 24) | Control (n=24) | *P* Value |
| Total | 5 | 14 | 0.007 |
| I cannot make a large cough | 1 | 1 | |
| I cannot move smoothly | 1 | 3 | |
| I cannot maintain the same position | 0 | 3 | |
| I cannot take a deep breath | 0 | 1 | |
| I cannot carry luggage | 1 | 2 | |
| I cannot sleep well | 1 | 1 | |
| I cannot change clothes easily | 1 | 3 | |
| None | 19 | 10 | |
| 3 Months after surgery (n total) | Ketamine (n = 22) | Control (n=22) | *P* Value |
| Total | 5 | 10 | 0.1 |
| I cannot walk a long distance | 1 | 5 | |
| I cannot carry luggage | 1 | 0 | |
| I cannot sleep well | 0 | 1 | |
| I am usually exhausted | 2 | 3 | |
| I cannot change clothes easily | 0 | 1 | |
| None | 17 | 12 | |
| 6 Months after surgery (n total) | Ketamine (n = 22) | Control (n=22) | *P* Value |
| Total | 4 | 9 | 0.09 |
| I cannot make a large cough | 0 | 1 | |
| I cannot maintain the same position | 0 | 1 | |
| I cannot carry luggage | 1 | 1 | |
| I am usually exhausted | 1 | 5 | |
| I cannot move smoothly | 1 | 1 | |
| I cannot move my shoulder | 1 | 0 | |
| None | 18 | 13 | |

*Effect of Ketamine Infusion on Thoracotomy Pain after Discharge from the Hospital*

Several studies examined the effect of ketamine on the prevention of long-term postoperative pain. Hayes *et al.*[14] demonstrated that low-dose ketamine, 0.5 mg/kg, followed by ketamine at a dose of 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$ for 72 h did not reduce acute postamputation pain at 3 and 6 days after surgery or persistent postamputation pain 6 months after surgery in patients who had been treated with intravenous morphine for postoperative pain. The results of the current study are similar to those of De Kock *et al.*,[15] who reported that giving intravenous ketamine in addition to epidural bupivacaine–sufentanil–clonidine anesthesia reduced the area of hyperalgesia at 24, 48, and 72 h after surgery and prevented the development of persistent pain 6 months after surgery. In an animal study with the chronic constriction injury model, mechanical hyperalgesia was transiently suppressed in the ketamine group.[16] The higher dose of ketamine infusion during surgery may suppress the central sensitization evoked by noxious stimuli traveling through C fibers and may contribute to the long-term postoperative pain status. However, the blood concentration of ketamine in our study was much smaller than that in the study of De Kock *et al.*,[15] who infused ketamine during surgery, and the blood concentration of ketamine in our study was approximately 20% of that which gave an antihyperalgesic effect in volunteers[17] and in kidney-donating surgery.[18] Because of lower concentration of ketamine during surgery, in current study, noxious stimulus of surgical maneuver might not be eliminated. In our study, among the ketamine group patients, the pain scores and the number of patients with pain were nearly unchanged throughout the observation period. However, in the control group, the number of patients with pain and their pain scores decreased over time, resulting in a comparable pain status in the two groups at 6 months after surgery. In the control group, the level of pain might have transiently increased after surgery and then gradually improved. The gradual reduction in pain in the control group patients suggests that the effect of ketamine on long-term pain, in our study, may have been related to suppression of epidural morphine–induced hyperalgesia.

One reason for the finding that there was a different pain status between the treatment groups for only a short period of time may be related to the dose of morphine administered during the study. De Kock *et al.*[15] reported that there was a significant reduction in postoperative morphine requirement *via* intravenous

patient-controlled analgesia after surgery in their ketamine-treated patients compared with the control patients. In contrast, our patients were given a nearly identical dose of morphine with a nonsteroidal antiinflammatory drug as the rescue analgesic. An animal study that demonstrated that fentanyl induces long-lasting hyperalgesia reported that the duration of the hyperalgesic state was proportional to the dose of fentanyl.[7] In the current study, an equivalent dose of morphine was administered to the two groups; therefore, morphine may have induced an opioid-related hyperalgesic state for only a relatively short period of time.

Another explanation for our finding that ketamine suppressed postoperative pain for a shorter period of time than in the study of De Kock *et al.* may be due to the difference in the procedure. Rogers *et al.*[19] demonstrated that long-term postthoracotomy pain may be induced in part by damage of the intercostal nerve upon stretching the ribs, which may induce pain similar to neuropathic pain. In the current study, approximately 80% of the patients felt an unpleasant sensation around the surgical wound during the 6-month postoperative period. In a previous study, ketamine infusion reduced the level of postamputation pain,[20] and in an animal study of chronic constriction injury, postinjury treatment with MK-801, another *N*-methyl-D-aspartate receptor antagonist, reduced the degree of mechanical hyperalgesia.[16] Based on these studies, we expected that the abnormal sensation on the wound felt by the ketamine-treated patients would disappear more quickly than that felt by the control patients. In the current study, during the 6-month study period, the number of patients who felt a burning or sharp sensation decreased; however, the numbers of patients who claimed to have a heavy feeling did not change and were comparable between the two groups. Boureau *et al.*[21] reported that some verbal descriptors such as burning or shooting tend to be used more often by patients with neuropathic pain than by patients with nonneuropathic pain. Some descriptors, such as heavy, were used by both the patients with neuropathic pain and those with nonneuropathic pain. A heavy feeling may be related not only to intercostal nerve damage but also to surgical procedures such as cutting the muscle. The number of patients who felt baseline pain at 6 months in the current study was similar to that in the study in which epidural analgesia was aggressively applied.[3] In the current study, acute pain was well controlled even in the control group, and the number of patients who had pain at 6 months after surgery was small. Comparable numbers of patients in the two groups described the unpleasant feeling on the wound as heavy, and this sensation may not be related to neural damage. Therefore, there is a small possibility that administering a higher dose of ketamine would reduce the incidence of long-term postoperative pain.

One limitation of this study was that the patient was asked to describe the sensation around the wound by verbal description. Asking the patient to describe the pain he or she feels in one word may not be sufficient to identify the patient's chronic pain status. In future studies, we may have to quantify the level of chronic pain using a pain questionnaire such as the McGill pain questionnaire.[22] Another limitation of this study was that the degree of improvement of pain by ketamine was relatively small. Farrar *et al.*[23] demonstrated that a drug has a clinically beneficial effect if it reduces pain intensity by 33% or if it reduces the NRS score by 2 (on a scale of 0–10). The difference in the mean NRS score at 3 months between the ketamine and control groups was only 1. We may have obtained this result because the NRS scores for pain at rest in the control group were relatively low, and the sample size of this study was small. A large clinical study that quantitatively evaluates chronic pain status is warranted.

In conclusion, very-low-dose ketamine infusion as an adjunct to morphine and ropivacaine analgesia during and after thoracotomy seems to reduce persistent pain after thoracotomy. There were no complications associated with ketamine infusion. Studies on the safety and efficacy of a higher dose of ketamine during surgical manipulation are warranted.

The authors appreciate the guidance of Kentaro Tsueda, M.D. (deceased, former Professor of Anesthesiology, University of Louisville School of Medicine, Louisville, Kentucky). The authors thank Daniel I. Sessler, M.D. (Professor of Anesthesiology, Outcomes Research Institute, University of Louisville School of Medicine, Louisville, Kentucky), and Nancy Alsip (Editor, Department of Anesthesiology, University of Louisville School of Medicine) for their assistance in preparing the manuscript.

## References

1. d'Amours RH, Riegler FX, Little AG: Pathogenesis and management of persistent postthoracotomy pain. Chest Surg Clin North Am 1998; 8:703–22

2. Katz J, Jackson M, Kavanagh BP, Sandler AN: Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996; 12:50–5

3. Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, Dilege S, Pembeci K: The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002; 94:11–5

4. Mao J, Price DD, Mayer DJ: Mechanisms of hyperalgesia and morphine tolerance: A current view of their possible interactions. Pain 1995; 62:259–74

5. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K: Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: A randomized double-blind study. ANESTHESIOLOGY 2000; 92:1624–30

6. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A: Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg 1993; 77:1161–5

7. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G: Long-lasting hyperalgesia induced by fentanyl in rats: Preventive effect of ketamine. ANESTHESIOLOGY 2000; 92:465–72

8. Suzuki M, Kinoshita T, Kikutani T, Yokoyama K, Inagi T, Sugimoto K, Haraguchi S, Hisayoshi T, Shimada Y: Determining the plasma concentration of ketamine that enhances epidural bupivacaine-and-morphine-induced analgesia. Anesth Analg 2005; 101:777–84

9. Javery KB, Ussery TW, Steger HG, Colclough GW: Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996; 43:212–5

10. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB: Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth 1998; 81:707–12

11. Edwards ND, Fletcher A, Cole JR, Peacock JE: Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia 1993; 48:124–7

12. Mao J, Price DD, Caruso FS, Mayer DJ: Oral administration of dextromethorphan prevents the development of morphine tolerance and dependence in rats. Pain 1996; 67:361–8

13. Sveticic G, Gentilini A, Eichenberger U, Luginbuhl M, Curatolo M,: Combinations of morphine with ketamine for patient-controlled analgesia: A new optimization method. ANESTHESIOLOGY 2003; 98:1195–205

14. Hayes C, Armstrong-Brown A, Burstal R: Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: A randomized, controlled trial. Anaesth Intensive Care 2004; 32:330–8

15. De Kock M, Lavand'homme P, Waterloos H: "Balanced analgesia" in the perioperative period: Is there a place for ketamine? Pain 2001; 92:373–80

16. Hudspith MJ, Harrisson S, Smith G, Bountra C, Elliot PJ, Birch PJ, Hunt SP, Munglani R: Effect of post-injury NMDA antagonist treatment on long-term Fos expression and hyperalgesia in a model of chronic neuropathic pain. Brain Res 1999; 822:220–7

17. Warncke T, Stubhaug A, Jorum E: Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. Pain 2000; 86:293–303

18. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32

19. Rogers ML, Henderson L, Mahajan RP, Duffy JP: Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002; 21:298–301

20. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS: The effect of ketamine on phantom pain: A central neuropathic disorder maintained by peripheral input. Pain 1996; 67:69–77

21. Boureau F, Doubrère JF, Luu M: Study of verbal description in neuropathic pain. Pain 1990; 42:145–52

22. Bruce J, Poobalan AS, Smith WC, Chambers WA: Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. Clin J Pain 2004; 20:70–5

23. Farrar JT, Berlin JA, Strom BL: Clinically important changes in acute pain outcome measures: A validation study. J Pain Symptom Manage 2003; 25:406–11