

## Randomized Trial

## Effects of Intraoperative Low-Dose Ketamine on Persistent Postsurgical Pain after Breast Cancer Surgery: A Prospective, Randomized, Controlled, Double-Blind Study

Christine Kang MD<sup>1</sup>, Ah-Reum Cho MD, PhD<sup>1</sup>, Kyung-Hoon Kim MD, PhD<sup>2</sup>, Eun-A Lee MD<sup>3</sup>, Hyeon-Jeong Lee MD, PhD<sup>1</sup>, Jae-Young Kwon MD, PhD<sup>1</sup>, Haekyu Kim MD, PhD<sup>1</sup>, Eunsoo Kim MD, PhD<sup>1</sup>, Ji-Seok Baik MD, PhD<sup>1</sup>, and Choongrak Kim MD, PhD<sup>4</sup>

From: <sup>1</sup>Department of Anesthesia and Pain Medicine, Medical Research Institute, Pusan National University Hospital, Busan; <sup>2</sup>Department of Anesthesia and Pain Medicine, Pusan National University Yangsan Hospital, Yangsan; <sup>3</sup>Department of Anesthesia and Pain Medicine, Hanyang Rheumatis Hospital, Busan; <sup>4</sup>Department of Statistics, Pusan National University, Busan, Republic of Korea.

Address Correspondence: Ah-Reum Cho, MD, PhD  
Department of Anesthesia and Pain Medicine and Medical Research Institute  
Pusan National University Hospital, Busan, Korea  
179 Gudok-ro, Seo-gu, Busan, 49241, Republic of Korea  
E-Mail: arco@pusan.ac.kr

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**Background:** Compared to acute postsurgical pain, studies regarding the role of ketamine in persistent postsurgical pain (PPSP) are limited.

**Objectives:** The aim of this clinical trial was to test if intraoperative low-dose ketamine without postoperative infusion would reduce PPSP development after breast cancer surgery.

**Study design:** We used a randomized, double-blinded, placebo study design.

**Setting:** This study was conducted at Pusan National University Hospital, Republic of Korea, between December 2013 and August 2016.

**Methods:** A total of 184 patients scheduled for breast cancer surgery were randomly assigned to either the control or ketamine group. Before skin incision, a bolus (0.5 mg/kg of ketamine or placebo), followed by a continuous infusion (0.12 mg/kg/h of ketamine or placebo), was administered until the end of the surgery. The patients were interviewed via telephone 1, 3, and 6 months after surgery. The first question was whether the patient had surgery-related pain. If answered affirmatively, questions from the Numeric Rating Scale for pain at rest (NRSr) and for coughing (NRSd) were also asked. Our primary outcome was the incidence of PPSP at 3 months after surgery.

**Results:** For PPSP analysis, 168 patients were included. The number of patients who experienced pain was significantly lower in the ketamine group at 3 months (86.9% in the control group vs 69.0% in the ketamine group,  $P = .005$ ) postoperatively. However, the NRSr and NRSd did not differ between the groups throughout the follow-up.

**Limitations:** There were no postoperative low-dose ketamine infusion groups to compare due to hospital regulations. Dosage of ketamine was too low to reduce the severity of PPSP. And by using propofol and remifentanyl for anesthesia, different results can be deduced with volatile anesthetics. Data from written questionnaires would have been more specific than telephone interviews for long-term assessment.

**Conclusions:** Though intraoperative low-dose ketamine without postoperative infusion significantly reduced the incidence of PPSP up to 3 months after breast cancer surgery, it failed to reduce clinically significant PPSP and improve patients' quality of life.

**Key words:** Analgesia, breast cancer, chronic pain, ketamine, mastectomy, morphine, pain, postoperative, propofol

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**A**lthough initially developed as an anesthetic, ketamine has recently gained importance in perioperative pain management (1-6), owing to its unique properties involving interactions with N-methyl-D-aspartate (NMDA) receptors (7),  $\mu$ -opioid receptors (8), and several others (9). The effects of ketamine on acute postsurgical pain (APSP) have been studied extensively; however, results are inconsistent, largely owing to the wide variability in study methodology (1,2,6). Recently, consensus guidelines on the use of ketamine in acute pain were published because of its growing use in perioperative pain management (10).

Compared to APSP, studies on the role of ketamine in persistent postsurgical pain (PPSP) are limited and underpowered (3-5). However, PPSP is a serious medical problem, as it lowers patient quality of life and contributes to medical expenses; it is therefore important to develop strategies to prevent the APSP-PPSP transition. A systematic review and meta-analysis showed that intravenous ketamine significantly reduced the risk of PPSP at 3 and 6 months (5). However, the researchers failed to suggest ketamine dosage regimens or timing (pre-emptive or preventive) to reduce PPSP. Additionally, they concluded that increasing ketamine doses does not consistently reduce PPSP. Moreover, subanesthetic ketamine doses may cause serious psychotomimetic complications, and indeed, the guidelines warn that postoperative ketamine infusion could be associated with psychotomimetic adverse effects (2,11). Therefore, this clinical trial aimed to test whether intraoperative low-dose ketamine without postoperative infusion would safely and effectively reduce PPSP development at 3 months after breast cancer surgery.

## METHODS

### Enrollment

The study was approved by the institutional review board of Pusan National University Hospital, Republic of Korea on April 12, 2013 (Busan, Republic of Korea, H-1303-009-016), and registered prior to patient enrollment in the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP), Clinical Research Information Service (CRiS) (ID - KCT0000962; Principal investigator: Ah-Reum Cho; Date of registration: December 18, 2013). The study was conducted between December 2013 and August 2016. Adult female patients aged 18 to 65 years with American Society of Anesthesiologists (ASA) physical status I and II, sched-

uled for elective unilateral breast cancer surgery, were approached for study participation. Exclusion criteria were a history of psychological problems; inability to use a patient-controlled analgesia (PCA) device or respond to the Numeric Rating Scale (NRS-11); a history of chronic pain management; current pain; morbid obesity (body mass index > 25 kg/m<sup>2</sup>), pregnancy or breast-feeding; contraindication to morphine or ketamine (history of uncontrolled hypertension, ill-treated hyperthyroidism, increased ocular pressure, allergy to both drugs, renal insufficiency, or hepatic disorders); enrollment in another clinical trial; and refusal. Patients received oral and written information about the protocol and written consent was obtained the day before the surgery by trial investigators.

### Randomization

Patients were randomly assigned to either the ketamine or control group according to a computer-generated simple randomization list, in a 1:1 ratio. On the morning of the surgery, each study drug was prepared, numbered, and sealed by our investigational pharmacy according to the schedule. One syringe contained 100 mg of ketamine (2 mg/mL) with 48 mL of 0.9% normal saline, and the other contained 50 mL of 0.9% normal saline. All syringes were labelled "study drug" and consecutively numbered. The intervention was blinded to all patients, investigators, and surgeons until all data analysis was completed.

### Intervention

During their pre-anesthesia evaluation, patients were instructed on the use of the PCA pump (The GemStar System, Abbott, IL, USA) to achieve comfort and assessed with the NRS-11 to measure pain (0 = no pain, 10 = worst pain). Patients were given 3 mg of intramuscular midazolam and 0.2 mg of glycopyrrolate as premedication 30 minutes before surgery. Anesthesia was induced by total intravenous anesthesia using target-controlled infusion (Orchestra® with Base Primera, Fresenius Kabi, France) with propofol and remifentanyl to reach 5  $\mu$ g/mL and 4 ng/mL of effect-site concentration (Ce), respectively. In order to ensure adequate and similar anesthesia between the groups, propofol was titrated to maintain a target Bispectral Index (BIS; Bispectral Index™, Aspect Medical System, Norwood, MA, USA) value between 40 and 50, and remifentanyl infusion rate was titrated between 2 and 4 ng/mL in order to keep mean arterial pressure within 20% of baseline. Hypotension (mean blood pressure <

60 mm Hg) or bradycardia (heart rate < 45 beats per minute) was treated by stepwise reductions in the remifentanyl infusion. Additional intravenous fluids were also administered by the responsible anesthesiologist. If these persisted for more than 5 minutes, the patient was treated with 5 to 10 mg of ephedrine or 0.5 mg of atropine intravenously. After tracheal intubation facilitated with rocuronium 0.8 mg/kg, the patients' lungs were mechanically ventilated to normocapnia with a mixture of 50% oxygen and air. Additional intraoperative rocuronium was administered as necessary and recorded. Between induction and skin incision, patients received a 0.25 mL/kg (0.5 mg/kg of ketamine or normal saline)-study drug bolus followed by continuous infusion at 0.06 mL/kg/h (0.12 mg/kg of ketamine or normal saline) until the end of surgery. Thirty minutes before the end of surgery, a loading dose of 0.1 mg/kg of morphine sulphate was administered along with 0.075 mg of palonosetron HCl. Intraoperative propofol, remifentanyl, and the study drug were discontinued at the end of surgery.

After extubation, a PCA pump was connected to the patient. It contained morphine sulphate 100 mg (20 mL) with 80 mL of normal saline (1 mg/mL morphine sulphate). The pump delivered 2-mL boluses with a lockout period of 5 minutes and a 4-hour limit of 20 mL. If the NRS-11 was more than 4 despite using the PCA, rescue medication (4 mg of morphine sulphate) was injected intravenously by a nurse in the postanesthetic care unit (PACU) and the general ward. The PCA was discontinued 72 hours postoperatively. All patients received oral pregabalin 150 mg 2 hours before surgery and 75 mg twice a day for 2 weeks from the first postoperative day. Ramosetron HCl (0.3 mg) was injected to treat moderate to severe postoperative nausea and vomiting (PONV).

### Outcome Measurements

All perioperative assessments were performed by trial investigators or trained nurses. Duration of anesthesia and surgery; total dose of propofol, remifentanyl, and the study drug; time to extubation (from discontinuation of the anesthetic drug to tracheal extubation); and use of intraoperative ephedrine or atropine were recorded.

The NRS-11 score at rest (NRSr) and on coughing or moving (NRSd), sedation assessment (using the Riker Sedation-Agitation Scale), recovery time (using the Aldrete score system), cumulative morphine consumption, PONV and the need for antiemetics, shivering, hallucinations, nightmares, and rescue medication

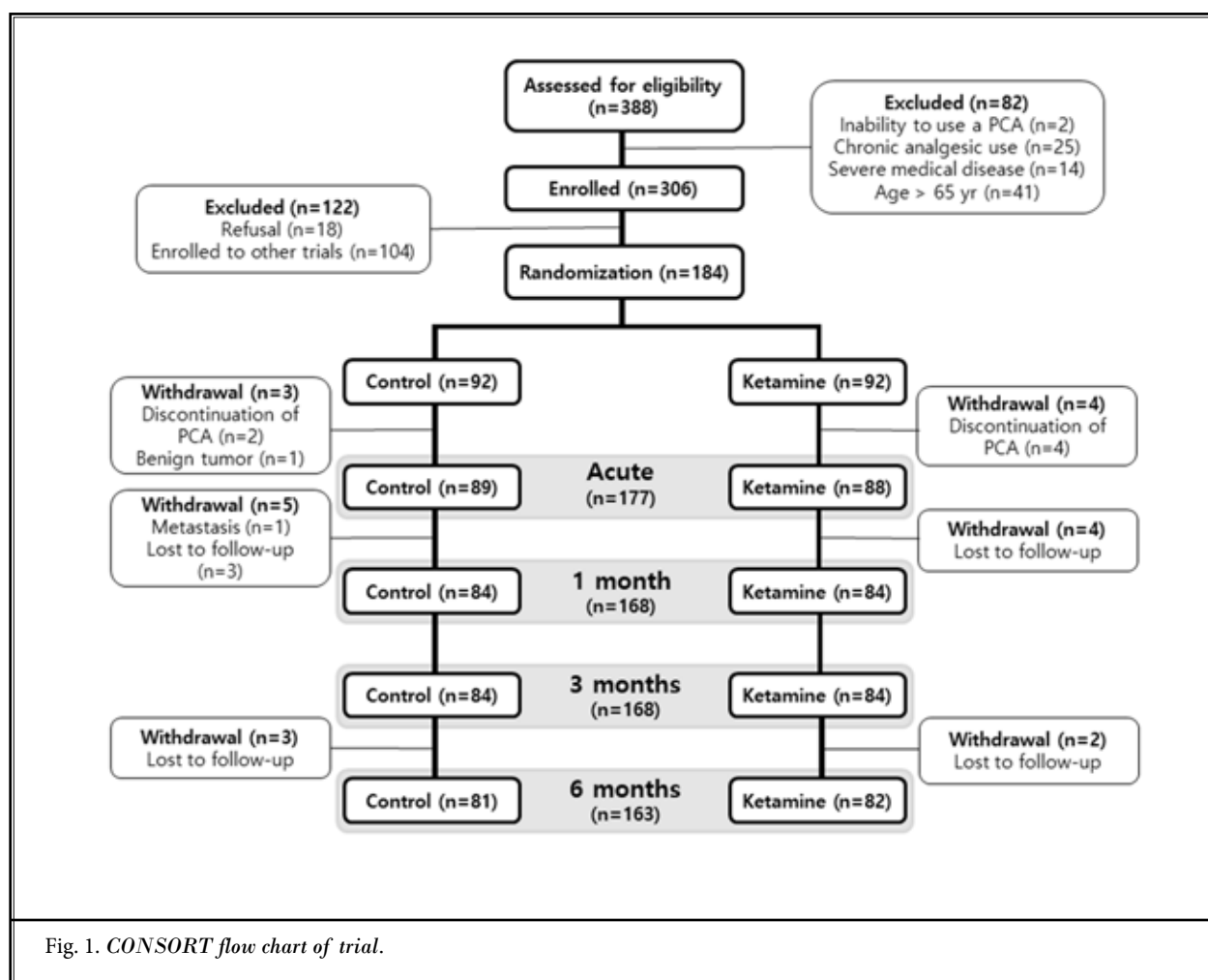
were recorded at 1 hour postoperatively in the PACU. Patients were discharged from the PACU after being monitored for 1 hour. The NRS-11 score at rest and on coughing; cumulative morphine consumptions; PONV and need for antiemetics; rescue medication; and the occurrence of anxiety, hallucinations, and nightmares were gathered 6, 12, and 24 hours postoperatively in the general ward.

The primary outcome was the incidence of PPSP at 3 months after breast cancer surgery. PPSP was defined as pain that developed after surgery and that lasted at least 3 months in the surgical site or innervation territory of a nerve situated in the surgical field (breast, shoulder, arm and back of the surgical side) (12). An investigator blinded to the treatment group and management interviewed patients via telephone 1, 3, and 6 months after surgery. The first question was whether the patient had surgery-related pain. If the answer was positive, the investigator asked for their NRSr and NRSd.

Additionally, we investigated whether the type of pain was neuropathic or not. Patients were asked to characterize their pain and whether abnormal sensation was present at the surgery site, according to the douleur neuropathique 4 (DN4) questionnaire (13). For assessing the quality of life, the questions were based on the EuroQoL 5-dimension health-related quality of life instrument (EuroQoL-5D) (14). We asked whether there were problems with performing self-care (washing or dressing oneself) and usual activities (work, study, housework, or leisure activities) to determine the impact of pain on daily life. We also asked about pain-induced impaired mobility of the ipsilateral arm and shoulder. We asked if the patient had made or was making any aggressive efforts to relieve pain (analgesics, massage, rehabilitation treatment, acupuncture, or herbal treatment). Finally, we asked if the patient had anxiety or depression. Information regarding chemotherapy, radiotherapy, and hormone therapy was collected from medical records. If patients did not respond to a phone call, 3 additional phone calls were made at different times of the day within a 2-week period. If the patient still could not be reached, they were dropped from the study.

### Statistical Analysis

We also conducted similar interviews for retrospective study with patients who had participated in our previous study in July 2011 via telephone (15,16). In the previous interview, we briefly asked patients



whether there was pain associated with surgery for more than 2 months after surgery (14). In total, 83.3% (10 of 12) patients in the control group and 64.3% (9 of 14) in the ketamine group experienced PPSP. Estimates indicated that a sample size of 166 patients (83 patients per group) would give a type I error of 5% and a power of 80%. Considering the drop-out rate of 10%, a total of 184 patients were required.

All continuous variables were tested for normal distribution using a Q-Q plot and Kolmogorov-Smirnov test. Data are expressed as means  $\pm$  standard deviations or 95% confidence interval, median  $\pm$  interquartile range, or number (%), as appropriate. The Student t test or the Mann-Whitney U test was used to compare continuous variables according to their distribution. Categorical variables were analyzed using chi-square or Fisher exact tests if any cell had expected counts less

than 5. *P* values < .05 were considered significant. Data analysis was performed using MedCalc for Windows, Version 13.2 (MedCalc Software, Ostend, Belgium) and SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

The flow diagram is shown in Fig. 1. We included 388 consecutive patients, and 306 consented to participate. Because 18 refused to participate and 104 were already enrolled in other trials, 184 patients were randomized. Three patients in the control group and 4 in the ketamine group were lost within 24 postoperative hours because the PCA was discontinued in 6 patients and histopathological examination revealed a benign tumor during surgery in one patient. Five patients in the control group and 4 patients in the ketamine group were lost within one month after surgery and 3 patients

in the control group and 2 patients in the ketamine group were lost between 3 and 6 months after surgery.

Patient characteristics and perioperative outcomes from 177 patients are shown in Table 1. There were no significant demographic differences between the 2 groups. There were no differences in PONV, rescue medication, and the occurrence of psychotomimetic complications. Extubation time was longer and shivering was less frequent in the ketamine group. Figure 2

shows the morphine consumption and the NRSr and NRSd at 1, 6, and 24 postoperative hours, and reveals no significant differences.

The number of patients who experienced pain was significantly lower in the ketamine group at one month (94% in the control group vs 84.5% in the ketamine group,  $P = .046$ ) and 3 months (86.9% in the control group vs 69.0% in the ketamine group,  $P = .005$ ) after surgery. However, the NRSr and NRSd were similar

Table 1. Patient characteristics and perioperative outcomes.

Variables	Control (n = 89)	Ketamine (n = 88)	P Value
ASA Physical Status (I/II)	62 (69.7)/27 (30.3)	58 (65.9)/30 (34.1)	.632
Age (yrs)	49.7 ± 7.2	50.8 ± 8.4	.376
Weight (kg)	59.1 ± 9.4	57.7 ± 7.4	.293
Height (cm)	157.6 ± 5.6	156.9 ± 5.5	.417
BMI (kg/m <sup>2</sup> )	23.8 ± 3.5	23.5 ± 3.0	.552
Duration of Surgery (min)	225.0 (157.5-265.0)	192.5 (150.0-250.0)	.197
Duration of Anesthesia (min)	255.0 (176.5-285.0)	225.0 (180.0-285.0)	.279
Propofol (mg)	1362.0 (986.0-712.5)	1415.0 (1062.5-1665.3)	.682
Remifentanyl (µg)	1871.0 (1218.5-2353.0)	1579.5 (1334.8-2097.5)	.210
Ketamine (mg)	0	50.5 (44.0-57.0)	< .001
Types of Surgery			
Mastectomy /s flap Surgery	12 (13.5)	7 (8.0)	.285
Mastectomy /c local flap	27 (30.3)	35 (39.8)	
Mastectomy /c LDMCF or EOMCF	50 (56.2)	46 (52.3)	
ALND	32 (36.0)	25 (28.4)	.283
Ephedrine or Atropine use	26 (29.2)	27 (30.7)	.831
Input (mL)			
Crystalloid	1200.0 (900.0-650.0)	1025.0 (800.0-500.0)	.055
Output (mL)			
Estimated blood loss	300.0 (200.0-350.0)	300.0 (200.0-387.5)	.647
Urine output	250.0 (150.0-460.0)	300.0 (152.5-480.0)	.726
Extubation Time (s)	720.0 (540.5-917.5)	894.5 (690.5-1116.8)	< .001
Recovery Time (min)	25.0 (15.0-35.0)	25.0 (20.0-35.0)	.328
PONV (0-24 h)			
None	51 (57.3)	48 (55.2)	.235
Mild	26 (29.2)	33 (37.9)	
Severe	12 (13.5)	6 (6.9)	
Requirement for Antiemetics (0-24 h)	14 (15.7)	18 (20.5)	.414
Shivering (0-1 h)	35 (39.3)	22 (25.0)	.041
Hallucination (0-24 h)	0 (0)	0 (0)	1.000
Nightmare (0-24 h)	2 (2.2)	2 (2.3)	1.000
Anxiety (6-24 h)	2 (2.2)	3 (3.4)	.682

Data are mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: ALND, axillary lymph node dissection; ASA, American Society of Anesthesiologists; BMI, body mass index; EOMCF, external oblique myocutaneous flap; LDMCF, latissimus dorsi myocutaneous flap; PONV, postoperative nausea and vomiting.

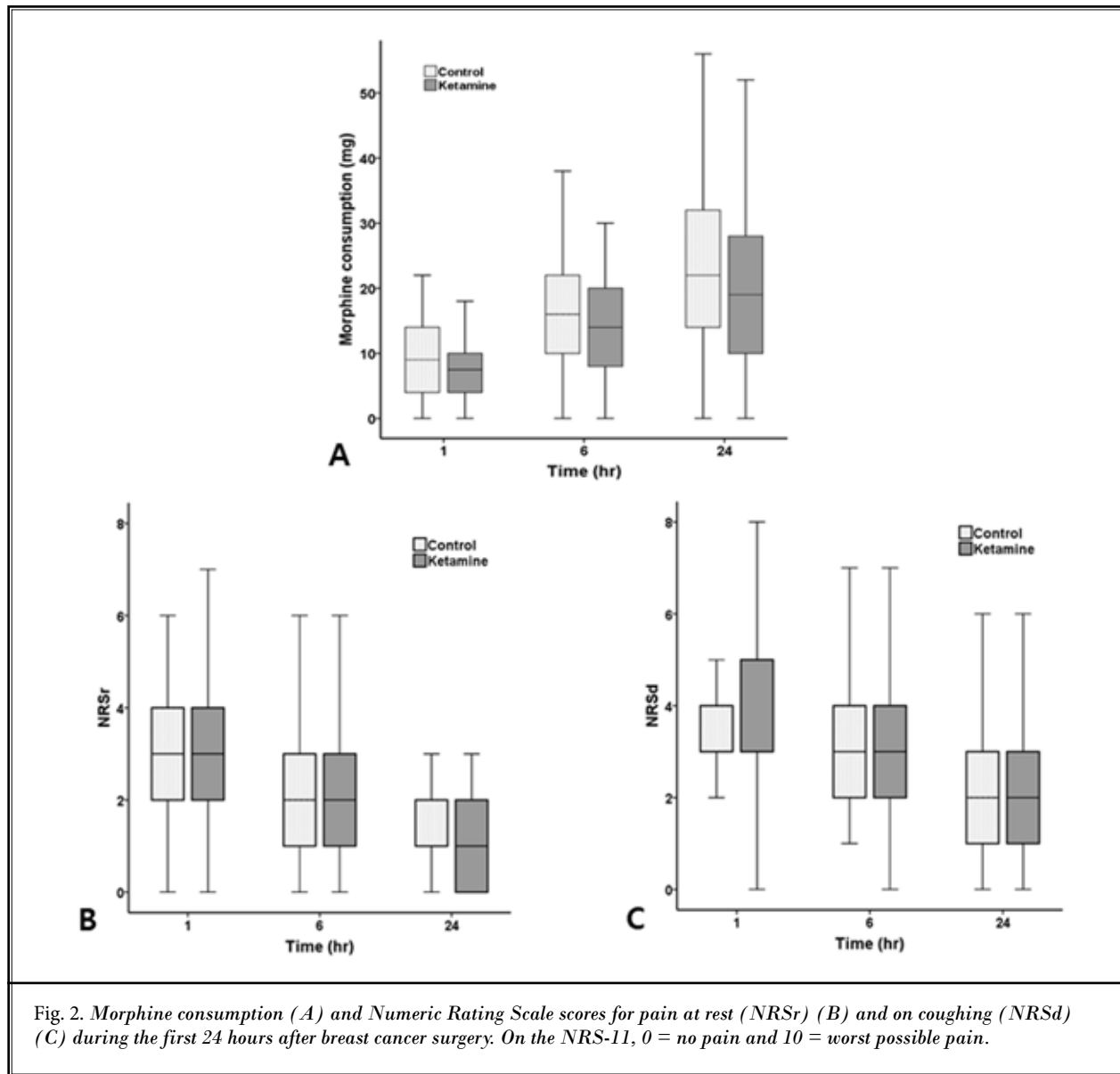


Fig. 2. Morphine consumption (A) and Numeric Rating Scale scores for pain at rest (NRSr) (B) and on coughing (NRSd) (C) during the first 24 hours after breast cancer surgery. On the NRS-11, 0 = no pain and 10 = worst possible pain.

between the groups throughout the follow-up assessment. When the NRS was categorized as mild (1-3), moderate (4-6), and severe (7-10) pain, there were significant differences between the groups at 6 months after surgery. Only 2.7% and 12.7% had moderate or severe pain at rest and on coughing, respectively, in the control group. In contrast, 24.3% and 30.4% had moderate or severe pain at rest and on coughing, respectively, in the ketamine group. According to DN-4 survey results, the number of patients experiencing neuropathic pain was not different between the 2

groups. There were no significant differences between the 2 groups in the number of patients who answered that they had pain management; limited arm or shoulder movement; daily life impairment; self-care difficulties; or depression (Table 3). There were no differences in cancer management between the 2 groups. Patients with PPSP received a significantly lesser dose of ketamine compared to patients without PPSP (Table 4). In addition, the number of patients with a DN-4 score  $\geq 4$  at one month postoperatively was significantly higher in patients with PPSP.

## Effect of Ketamine on Persistent Postsurgical Pain

Table 2. The assessment of postsurgical pain at 1, 3, and 6 months after surgery

Variables	After 1 Month			After 3 Months			After 6 Months		
	Control (n = 84)	Ketamine (n = 84)	P Value	Control (n = 84)	Ketamine (n = 84)	P Value	Control (n = 81)	Ketamine (n = 82)	P Value
Number of Patients who Experienced Pain	79 (94.0)	71 (84.5)	.046	73 (86.9)	58 (69.0)	.005	55 (67.9)	46 (56.1)	.121
NRSr	1.5 (0-3.0)	1.0 (0-3.0)	.667	1.0 (0-2.0)	1.0 (0-2.0)	.696	0 (0-1.0)	0 (0-2.0)	.929
NRSd	3.0 (2.0-4.0)	3.0 (1.0-4.0)	.168	2.0 (1.0-3.0)	2.0 (0-3.0)	.119	1.0 (0-3.0)	1.0 (0-3.0)	.474
Severity of Pain									
Pain at rest			.996			.417			.025
Mild	49 (79.0)	44 (78.6)		45 (86.5)	41 (82.0)		36 (97.3)	25 (75.8)	
Moderate	12 (19.4)	11 (19.6)		6 (11.5)	9 (18.0)		1 (2.7)	6 (18.2)	
Severe	1 (1.6)	1 (1.8)		1 (1.9)	0 (0.0)		0 (0.0)	2 (6.1)	
Pain on Coughing			.835			.199			.014
Mild	49 (62.0)	46 (64.8)		57 (78.1)	41 (70.7)		48 (87.3)	32 (69.6)	
Moderate	25 (31.6)	22 (31.0)		14 (19.2)	17 (29.3)		7 (12.7)	8 (17.4)	
Severe	5 (6.3)	3 (4.2)		2 (2.7)	0 (0.0)		0 (0.0)	6 (13.0)	
DN-4 Score ≥ 4	11 (13.1)	5 (6.0)	.115	5 (6.0)	3 (3.6)	.720	4 (4.9)	1 (1.2)	.210

Data are number (%) or median (interquartile range).

Abbreviations: DN-4, douleur neuropathique 4; NRSd, Numeric Rating Scale on coughing; NRSr, Numeric Rating Scale at rest.

Table 3. Quality of life and cancer treatment.

Variables	After 1 Month			After 3 Months			After 6 Months		
	Control (n = 84)	Ketamine (n = 84)	P Value	Control (n = 84)	Ketamine (n = 84)	P Value	Control (n = 81)	Ketamine (n = 82)	P Value
Pain Management	6 (7.1)	10 (11.9)	.282	6 (7.1)	5 (6.0)	.771	8 (9.9)	4 (4.8)	.222
Disability of Arm and Shoulder	26 (31.0)	27 (32.1)	.868	11 (13.1)	17 (20.2)	.214	8 (9.9)	11 (13.4)	.482
Affecting Daily Life	4 (3.0)	2 (2.4)	.682	4 (4.8)	1 (1.2)	.367	1 (1.2)	1 (1.2)	1.000
Affecting Self-care	19 (22.6)	15 (17.9)	.442	5 (6.0)	6 (7.1)	.755	4 (4.9)	7 (8.5)	.360
Depression									.801
None	71 (84.5)	75 (89.3)	.635	69 (82.1)	75 (89.3)	.311	69 (85.2)	72 (87.8)	
Mild	12 (14.3)	8 (9.5)		14 (16.7)	9 (10.7)		10 (12.3)	9 (11.0)	
Severe	1 (1.2)	1 (1.2)		1 (1.2)	0 (0)		2 (2.5)	1 (1.2)	
Chemotherapy with Paclitaxel	4 (4.8)	2 (2.4)	.682	5 (6.0)	2 (2.4)	.443	21 (25.9)	22 (26.8)	.896
Radiotherapy	4 (4.8)	4 (4.8)	1.000	16 (19.0)	16 (19.0)	1.000	39 (48.1)	36 (43.9)	.587
Hormone therapy	10 (12.2)	9 (10.7)	.764	15 (17.9)	15 (17.9)	1.000	34 (43.0)	28 (34.1)	.246

Data are number (%).

## DISCUSSION

Our study revealed that intraoperative ketamine could reduce the incidence of PPSP at 3 months after breast cancer surgery. However, the NRSr and NRSd did not differ between groups at 6 months after surgery. Also, the incidence of moderate and severe pain, representing clinically significant PPSP, was similar between the 2 groups at 1 and 3 months after surgery, while it occurred more frequently in the ketamine group at 6 months after surgery. Because the definition of PPSP in

our study did not include the severity of pain (12), mild pain was also included in PPSP. Mild pain does not cause functional disability in the patients' daily lives; thus our result showed no difference in quality of life between the control and ketamine groups. Considering that the recent definition of PPSP reflects significant impact on the patient's physical, psychological, or socio-economic well-being (17), it is difficult to say that the incidence of clinically significant PPSP was reduced by ketamine in our study. As physicians, our focus is usually on moder-



Table 4. Patient characteristics and clinical data for patients with or without persistent postsurgical pain at 3 months after breast cancer surgery.

Risk Factor Variables	Patients Without Chronic Pain (n = 37)	Patients With Chronic Pain (n = 131)	P Value
Age (yrs)	48.1 ± 9.1	50.1 ± 7.5	.163
Weight (kg)	57.7 ± 9.0	58.7 ± 8.5	.506
Height (cm)	157.6 ± 5.6	157.3 ± 5.4	.766
BMI (kg/m <sup>2</sup> )	23.2 ± 3.3	23.7 ± 3.2	.387
Remifentanyl (µg)	1674.0 (1287.5-2177.0)	1775.0 (1249.0-2246.0)	.738
Propofol (mg)	1399.0 (983.5-1614.5)	1370.0 (1052.0-1671.0)	.812
Ketamine (mg)	54.6 (45.8-64.9)	49.2 (0-59.5)	.007
Duration of Surgery (min)	205.0 (150.0-250.0)	215.0 (145.0-255.0)	.762
Duration of Anesthesia (min)	240.0 (180.0-285.0)	240.0 (165.0-285.0)	.948
Type of Surgery			.862
Mastectomy without flap surgery	3 (8.1)	14 (10.7)	
Mastectomy with local flap	13 (35.1)	48 (36.6)	
Mastectomy with LDMCF or EOMCF	21 (56.8)	69 (52.7)	
ALND	12 (32.4)	42 (32.1)	.966
Postoperative 24 h Morphine Consumption (mg)	21.5 (18.0)	22.8 (13.8)	.651
DN-4 Score ≥ 4 at 1 Month After Surgery	0 (0)	16 (12.2)	.024
Chemotherapy with Paclitaxel	1 (2.7)	5 (4.6)	.614
Radiotherapy	6 (16.2)	26 (19.8)	.619
Hormone Therapy	6 (16.2)	26 (19.8)	.619

Data are mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; DN-4, douleur neuropathique 4; EOMCF, external oblique myocutaneous flap; LDMCF, latissimus dorsi myocutaneous flap

ate and severe pain and we consider these as clinically relevant; as patients, mild pain can be uncomfortable, and relieving the patient of that pain can be meaningful. Therefore, though clinically irrelevant, we can interpret that ketamine is effective at increasing the proportion of patients who were pain-free 3 months after surgery.

There were no differences in acute pain scores and cumulative morphine requirements between the control and ketamine groups. Why acute pain did not decrease in the ketamine group in our study is not clear. It is known that the efficacy of ketamine in APSP may be evident in patients with severe postoperative pain (10). The expected pain after breast cancer surgery is mild to moderate depending on the extent of the surgery. Moreover, all patients were administered perioperative pregabalin, which would further reduce postoperative pain (18), masking the benefit of ketamine on APSP. Second, several studies showed that ketamine reduced postoperative opioid requirements only in opioid-tolerant patients, not in opioid-naïve patients (19,20).

In addition, previous studies with remifentanyl-based anesthesia have reported that the analgesic mechanism of ketamine inhibits remifentanyl-induced hyperalgesia (21,22). However, in our study, the total amount of remifentanyl did not differ significantly between the 2 groups because the ketamine dose was not enough to affect hemodynamics. Moreover, considering that we excluded patients with chronic pain management, the role of perioperative ketamine on APSP would be more evident in the situation of hyperalgesia and opioid tolerance through NMDA antagonism (22,23).

According to our study, ketamine delayed the extubation time about 3 minutes without prolonging the recovery time. Ketamine is known to increase BIS only for a few minutes after a 0.5-mg/kg bolus injection followed by a 1.0-mg/kg/h infusion (24). Propofol infusion was guided by BIS in our study, showing no difference in the total propofol dose between the 2 groups. Therefore, although delayed extubation time may be induced by ketamine, it is not clinically significant because the recovery time was not prolonged. Postoperative shiver-



ing was prevented by ketamine in our study. This is in line with the other previous study that demonstrated that 0.5 mg/kg of ketamine approximately 20 minutes before the end of surgery effectively prevented postoperative shivering (25).

There are currently no recommendations regarding an adequate dose of ketamine to prevent the transition from APSP to PPSP. The major concern in the analgesic use of ketamine is the dosage. We chose intraoperative low-dose ketamine without postoperative infusion because of safety considerations and the hospital regulations. Although only intraoperative low-dose ketamine was injected in our study, the incidence of PPSP at 3 months after surgery was reduced. Both intraoperative and postoperative periods are potential targets for a preventive approach in reducing the transition to pain chronicity. However, a recent meta-analysis showed that when ketamine was administered postoperatively there was no increase in efficacy compared to when it was only administered intraoperatively (5).

Previous studies have shown inconsistent results as to whether low-dose ketamine could prevent PPSP development (3,4,26). The limitation of many of these previous studies is that measuring the incidence of PPSP was not their primary goal. However, the primary objective of our study was to determine the incidence of PPSP based on a sample size calculation that used data from our previous retrospective survey (15,16). Two previous studies have been designed to investigate the incidence of PPSP as the primary outcome in patients with thoracotomy (4,26). Suzuki and colleagues (26) showed that low-dose ketamine potentiated morphine-ropiacaine analgesia and reduced the incidence of PPSP at 3 months after thoracotomy. In contrast, Duale and colleagues (4) showed that perioperative ketamine infusion failed to prevent chronic neuropathic pain after thoracotomy; however, the timing of the primary outcome was 6 months after thoracotomy. This result is consistent with our study and with the study by Suzuki and colleagues (26), which also revealed that the beneficial analgesic effect of ketamine was no longer significant 6 months after surgery.

Among the results of our study, the one that is most difficult to interpret is the fact that the incidence of moderate to severe pain was significantly higher in the ketamine group at 6 months after surgery. We assume that pain at 6 months after breast cancer surgery would not clearly reflect the analgesic effect of ketamine because, by this time point, many of our patients had had to undergo chemotherapy, hormone therapy,

and radiotherapy. Radiotherapy and chemotherapy have been suspected of increasing the risk of PPSP after breast cancer surgery (27,28). Studies have shown that 15% of patients with treated breast cancer suffer moderate to severe PPSP from 6 months to one year after surgery (29,30). In our study, 8.6% (7 of 81) of patients in the control group and 16.3% (14 of 82) of patients in the ketamine group suffered moderate to severe PPSP 6 months after surgery. This higher incidence raises the question of whether ketamine was responsible or not. It is difficult to analyze because the number of patients with moderate to severe pain is too small.

There are several limitations in our study. Our goal was to demonstrate that intraoperative low-dose ketamine without postoperative infusion could reduce the incidence of PPSP. The results would be easier to interpret if we had used a third group; that is, an intraoperative and postoperative low-dose ketamine infusion group. However, we could not include this third group because of a hospital regulation mandating that ketamine infusion in the general ward needs to be monitored judiciously by trained personnel. We believe that many hospitals would have environments and regulations similar to our hospital. Although we do not know whether additional postoperative infusion would have improved our result or not, intraoperative low-dose ketamine alone may have favorable effects on PPSP after breast cancer surgery.

Our result showed a discrepancy in that the control group reported more pain at 1 and 3 months after surgery, even though the NRS-11 values did not differ between the 2 groups. This is one of the limitations of our study, namely that clinically significant pain – which is moderate to severe pain – was not reduced in the ketamine group. More PPSP developed in the control group, however, and most of them had mild pain, which would not impair their ordinary functions. This is presumably because the ketamine dose was not enough to reduce the severity of PPSP. Despite the limitations, our study may be meaningful because, even at a very low dose, ketamine prevented the development of PPSP by increasing the proportion of patients who were pain-free. This suggests that increasing the dose of ketamine may reduce the severity of PPSP.

Third, all patients were anesthetized with propofol and remifentanyl in our study. Since many studies have shown that anesthetics influence postoperative pain (15,31), the results would have been different if we had used volatile anesthetics. However, we prefer to use propofol when remifentanyl-based anesthesia is chosen

because propofol prevents opioid-induced hyperalgesia (32).

We did not use validated written questionnaires for long-term assessment. Using a validated questionnaire would provide quantifiable answers that are relatively easy to analyze. Also, quantified scores make it easy to compare results between studies. However, it is difficult to meet patients and administer questionnaires within a limited period of time. It is easier to lose contact with follow-up patients if the follow-up period is longer. Moreover, the higher the drop-out rate, the lower the power of the study. Therefore, we decided to do telephone interviews to reduce drop-out rates and collect as much long-term data as possible. Our telephone interview was designed according to DN-4 and EuroQoL-5D, which is a standardized measure of health status (13,14).

## CONCLUSIONS

In conclusion, intraoperative low-dose ketamine without postoperative infusion significantly reduced the incidence of PPSP up to 3 months after breast cancer surgery. However, our study failed to reduce APSP and clinically significant PPSP. APSP, while important, can be treated adequately with proven drugs when it presents. In contrast, once PPSP develops, the treatment is difficult and may come too late. Further studies should be focused on the role of ketamine in preventing the chronification of pain, and on designing large, multicenter studies with standardized timing and dosing of ketamine.

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## Contributorship Statement

Christine Kang: This author contributed to study design/planning, study conduct, and writing and revising paper.

Ah-Reum Cho: This author contributed to study design/planning, data analysis, and writing and revising paper.

Eun-A Lee: This author contributed to study design/planning, study conduct, and revising paper.

Kyung-Hoon Kim: This author contributed to study design/planning and revising paper.

Hyeon-Jeong Lee: This author contributed to study design/planning, data analysis, and revising paper.

Jae-Young Kwon: This author contributed to study design/planning and revising paper.

Haekyu Kim: This author contributed to data analysis and revising paper.

Eun-Soo Kim: This author contributed to study conduct and revising paper.

Ji-Seok Baik: This author contributed to data analysis and revising paper.

Choongrak Kim: This author contributed to data analysis and revising paper.

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