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# *Preemptive Analgesia by Intravenous Low-dose Ketamine and Epidural Morphine in Gastrectomy*

## *A Randomized Double-blind Study*

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***Background:*** **Morphine and ketamine may prevent central sensitization during surgery and result in preemptive analgesia. The reliability of preemptive analgesia, however, is controversial.**

***Methods:*** **Gastrectomy patients were given preemptive analgesia consisting of epidural morphine, intravenous low-dose ketamine, and combinations of these in a randomized, double-blind manner. Postsurgical pain intensity was rated by a visual analog scale, a categoric pain evaluation, and cumulative morphine consumption.**

***Results:*** **Preemptive analgesia by epidural morphine and by intravenous low-dose ketamine were significantly effective but not definitive. With epidural morphine, a significant reduction in visual analog scale scores at rest was observed at 24 and 48 h, and morphine consumption was significantly lower at 6 and 12 h, compared with control values. With intravenous ketamine, visual analog scale scores at rest and morphine consumption were significantly lower at 6, 12, 24, and 48 h than those in control subjects. The combination of epidural morphine and intravenous ketamine provided definitive preemptive analgesia: Visual analog scale scores at rest and morphine consumption were significantly the lowest at 6, 12, 24, and 48 h, and the visual analog scale score during movement and the categoric pain score also were significantly the lowest among the groups.**

***Conclusion:*** **The results suggest that for definitive preemptive analgesia, blockade of opioid and N-methyl-D-aspartate receptors is necessary for upper abdominal surgery such as gastrectomy; singly, either treatment provided significant, but not definitive, postsurgical pain relief. Epidural morphine may affect the spinal cord segmentally, whereas intravenous ketamine may block brain stem sensitization *via* the vagus nerve during upper abdominal surgery. (Key words: Epidural analgesia; heterosegmental innervation; segmental innervation.)**

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SENSORY neurons are more sensitive to peripheral inputs after activation of C fibers by a noxious stimuli, a process called *central sensitization*.[1,2] Another mechanism activating spinal sensory neurons, "wind up,"[3] is observed after repeated stimulation of C fibers. These sensitizations induce c-*fos* expression in sensory neurons,[4] and are associated with the activation of *N*-methyl-D-aspartate (NMDA) receptors[2,4] and neurokinin receptors.[5,6] Protection of sensory neurons against central sensitization may offer relief from pain occurring after injury or surgery, according to Wall.[7] Based on this theory, preemptive analgesia has been advocated as an effective tool to manage postsurgical pain.[8,9]

The mechanisms involved in preemptive analgesia may include intercepting nociceptive input, increasing the threshold for nociception, and blocking NMDA receptor activation.[1-9] Therefore, regional anesthesia, analgesia, or NMDA receptor antagonists have been used in studies of preemptive analgesia.[8,9] These methods have shown the validity of preemptive analgesia in animal experiments.[4,10,11] As noted by Bridenbaugh[12] and Dahl and Kehlet,[13] however, many clinical studies of preemptive

analgesia have failed to show clinically relevant relief of postsurgical pain. For effective preemptive analgesia, both interception of nociceptive input and blockade of NMDA activation may be necessary.

Abdominal organs are innervated multisegmentally by both the spinal nerve and the vagus nerve.[14] Schuligoi *et al.*[15] demonstrated that gastric nociception is mediated by the vagus nerve and induces c-*fos* expression in brain stem neurons. Bon *et al.*[16] suggested that brain stem neurons express c-*fos* after visceral nociception, and that the dorsal vagal complex in the brain stem is the main visceral pain center. Meanwhile, Segawa *et al.*[17] suggested that the phrenic nerve (C3–C5) mediates stress responses arising from the upper abdominal organs. In our recent results,[18] preemptive analgesia with epidural morphine was insufficient to block pain from surgery involving laparotomy (gastrectomy, hysterectomy, appendectomy, and herniorrhaphy).

Generally, drugs given intravenously affect the brain, spinal cord, and peripheral nervous system; hydrophilic drugs, such as ketamine and morphine, given epidurally usually exert larger effects on the spinal cord than the brain. If a small dose of these drugs is administered into the epidural space, effects on the spinal cord may predominate, and systemic or supraspinal effects may be lacking. In abdominal surgery, therefore, either segmental analgesia with only epidural analgesia or supraspinal analgesia with only intravenous analgesia may show little preemptive effect because of the lack of a spinal or supraspinal effect, respectively. A combination of spinal and supraspinal analgesia has the potential to produce preemptive analgesia. We reasoned that clinical studies[12] have not been successful because the brain stem becomes sensitized to pain in spite of segmental preemptive treatment.

We evaluated the effect of preemptive treatments with epidural morphine, intravenous low-dose ketamine, and combinations of the two on postsurgical pain. We chose not to include a higher systemic dose of ketamine because, if analgesics or NMDA blockers are administered systemically, the clinical assessment of postsurgical pain may be difficult because of the aftereffects of the drug. We examined the effectiveness of preemptive analgesia by combinations of these treatments during major abdominal surgery, gastrectomy.

## Patients and Methods

We obtained approval from the institutional committee of Teikyo University School of Medicine for human investigation and informed consent from individual patients. All patients undergoing elective surgery for distal or total gastrectomy because of stomach cancer were considered for inclusion in the study. None of the patients had severe hepatic, renal, cardiovascular, or psychological disorders (they were classified as American Society of Anesthesiologists physical status I or II).

### *Presurgical Education, Epidural Cannulation, and General Anesthesia*

A day before surgery, patients were taught how to complete the visual analog scale (VAS) interview and to use the patient-controlled analgesia (PCA) pump (PC1071PCA; Baxter, Deerfield, IL). Patients who could not rate the VAS score or use the PCA pump, including those with dementia, deafness, poor eyesight, or parkinsonism, were excluded from the study.

Each patient was premedicated with atropine, 0.01 mg/kg, and hydroxyzine, 1 mg/kg. Before the induction of general anesthesia, a 1-mm polyethylene catheter was inserted into the epidural space at the T8–T9 level. The epidural catheter was available for preemptive as well as postsurgical epidural analgesia.

All patients received general anesthesia with inhalation of 1 or 2% sevoflurane and 30% oxygen–70% nitric oxide gas mixture and intravenous vecuronium, 0.08 mg $\cdot$ $kg^{-1} \cdot h^{-1}$, after tracheal intubation with intravenous propofol, 2 mg/kg, and vecuronium, 0.16 mg/kg. At the completion of skin closure, muscle relaxation was reversed with atropine, 0.01 mg/kg, and neostigmine, 0.03 mg/kg, and patients were extubated after confirmation of absence of hypercapnia (high end-tidal carbon dioxide concentration), or decreased respiratory rate ($< 12$ breaths/min).

### *Patient Randomization and Preemptive Analgesia*

According to a computer-generated table of random number assignments, each patient was assigned to one of four groups (table 1). One group received epidural morphine and intravenous saline. A second received intravenous low-dose ketamine and epidural saline as a placebo. Both epidural morphine and intravenous low-dose ketamine were tested in a combination group, and a control group represented infused intravenous saline and epidural saline.

Epidural morphine was administered as a bolus dose of 0.06 mg/kg 40 min prior to skin incision and then maintained continuously until skin closure at a dosage of 0.02 mg $\cdot$ $kg^{-1} \cdot h^{-1}$. Intravenous ketamine was administered as a bolus dose of 1.0 mg/kg, 10 min prior to skin

**Table 1. Summary of Treatment Groups**

| Group | Age (yr) | N | Sex (F/M) | Body Weight (kg) | Height (m) | Surgery Duration (min) | Blood Loss (ml/kg) |
|---|---|---|---|---|---|---|---|
| MORep | 64 ± 10 | 30 | 12/18 | 54.5 ± 8.6 | 1.59 ± 0.08 | 246 ± 93 | 5.2 ± 3.6 |
| KETiv | 62 ± 14 | 29 | 10/19 | 55.8 ± 8.6 | 1.58 ± 0.09 | 233 ± 138 | 5.9 ± 7.2 |
| COMB | 66 ± 9 | 31 | 11/20 | 53.9 ± 9.9 | 1.55 ± 0.08 | 239 ± 121 | 5.8 ± 5.6 |
| CTL | 63 ± 13 | 31 | 14/17 | 56.7 ± 9.4 | 1.54 ± 0.11 | 236 ± 124 | 4.2 ± 3.8 |

There were no significant differences in the respective values among the groups (chi-square test (sex) and one-way analysis of variance.
MORep = epidural morphine group; KETiv = intravenous ketamine group; COMB = combination group; CTL = control group.

incision, and then maintained continuously until skin closure at a dosage of 0.5 mg · $kg^{-1}$ · $h^{-1}$. Immediately after surgery, the epidural morphine and combination groups received bolus naloxone, 0.008 mg/kg, administered intravenously, to erase the aftereffect of morphine. The other groups received saline as a placebo. Based on the computer-generated random sequence, the study supervisor prepared the drug solutions, which were sealed in an envelope and transferred to the anesthesiologist blinded to the solutions.

*Postsurgical Pain Management and Pain Assessment by a Blinded Observer*

After total recovery of awareness, which was defined as a patient's ability to open his or her eyes, grip a finger, and breathe deeply on request, the PCA pump was set to inject a 0.2-mg bolus dose of epidural morphine, with a lockout time of 15 min between doses. There was no background infusion or maximal dose, and the pump was removed 48 h after surgery. The cumulative dose of morphine used was noted at 6, 12, 24, and 48 h. No other analgesics were given during the perisurgical period.

Another blinded physician assessed spontaneous postsurgical pain intensity at rest using the VAS at 6, 12, 24, and 48 h after surgery. Pain during movement (trying to change position) also was assessed using the VAS at 12 h after surgery. The pain intensity was rated carefully with strict discrimination between pains at rest and during movement. Patients described their maximum pain within the 48 h after surgery using a categoric scale (3 = severe, requiring use of the PCA pump; 2 = bearable, not requiring PCA; 1 = slight; 0 = nil).

*Statistical Analysis*

Independence was analyzed using the chi-square test. Parametric data were analyzed using the one-way analysis of variance in combination with the Tukey test. Nonparametric data were analyzed using the two-factor mixed-design analysis of variance with repeated measurement on one factor, or the Kruskal–Wallis test in combination with the Dunn test. $P < 0.05$ was considered significant. The values were expressed as the mean ± SD or median with first and third quartiles (Q1 and Q3).

## Results

There were no significant differences in age, gender, surgical duration, or blood loss among the groups (table 1). All patients recovered awareness within 20 min after skin closure, and patients could use the PCA pump freely.

In the epidural morphine group, a significant reduction in postsurgical VAS scores at 24 and 48 h was observed compared with the control group. Postsurgical cumulative morphine consumption in the epidural morphine group was significantly lower than that in the control group at 6, 12, 24, and 48 h (figs. 1 and 2).

In the intravenous low-dose ketamine group, postsurgical VAS scores were significantly lower at 6, 12, 24, and 48 h, and cumulative morphine consumption was significantly lower at 6, 12, 24, and 48 h, than in the control group (figs. 1 and 2).

In the combination group, preemptive analgesia was definitive; VAS scores at rest and cumulative morphine consumption were significantly the best among the groups at every time point observed (figs. 1 and 2).

The VAS scores during movement in the epidural morphine and combination groups were decreased significantly compared with the control group, and the score in the combination group was significantly the lowest among the groups (fig. 3). In the combination group, the categoric pain score was significantly the lowest among the groups (table 2).

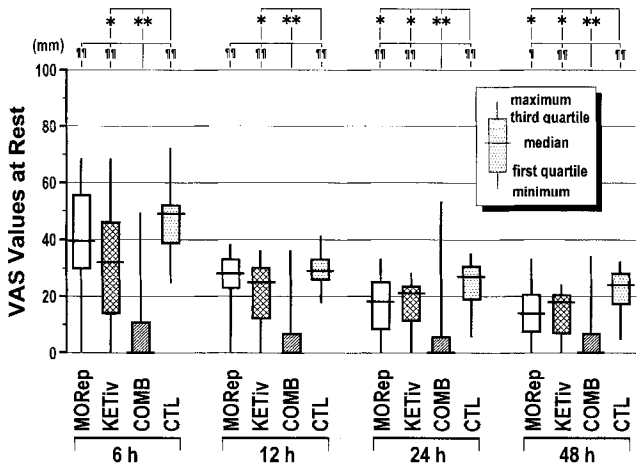


**Fig. 1. Visual analog scale scores after surgery. Scores were lowest at all time points in the combination group, which received epidural morphine and intravenous ketamine; the preemptive effects of epidural morphine and intravenous ketamine were significant but insufficient. The two-factor mixed-design analysis of variance with repeated measurement on one factor and the Dunn test were used. *$P$ < 0.05, **$P$ < 0.005 *versus* the control group. ¶$P$ < 0.05, ¶¶$P$ < 0.005 *versus* the combination group. See table 1 for a definition of abbreviated terms.**

## Discussion

Preemptive analgesia was achieved in this study, but its effectiveness varied among the treatment groups. In particular, preemptive analgesia after treatment with combination of epidural morphine and low-dose intravenous ketamine was most effective. Also, we observed a significant reduction in VAS scores after treatment singly with epidural morphine or low-dose intravenous ketamine, but the potency of these treatments was significantly inferior to that of the combination. These phenomena were seen consistently among the results of the VAS assessments of pain intensity at rest and during movement, the cumulative morphine consumption, and the categoric pain scores.

In abdominal surgery, previous results have suggested an insufficient effect after single use of epidural morphine[19] or intravenous ketamine.[20–22] Blockades of no-

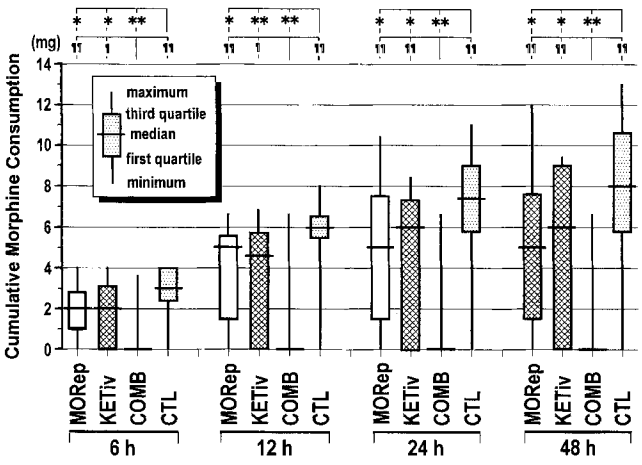


**Fig. 2. Cumulative morphine consumption. Consumption was lowest at all time points in the combination group, which received epidural morphine and intravenous ketamine. Statistics are the same as in figure 1. The two-factor mixed-design analysis of variance with repeated measurement on one factor and the Dunn test were used. *$P$ < 0.05, **$P$ < 0.005 *versus* the control group. ¶$P$ < 0.05, ¶¶$P$ < 0.005 *versus* the combination group. See table 1 for a definition of abbreviated terms.**

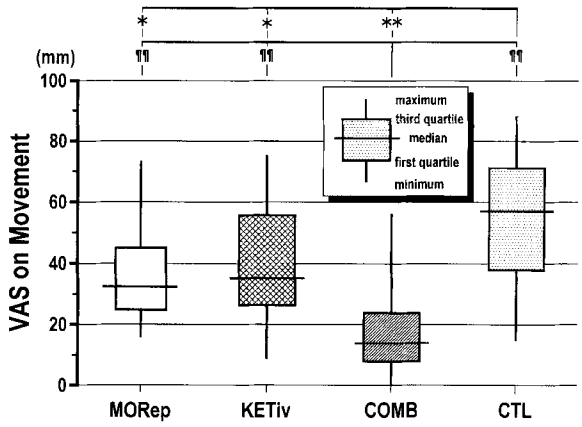


**Fig. 3. Visual analog score during movement. Pain during movement (trying to change position), assessed using the visual analog scale at 12 h after surgery, was lowest in the combination group, which received epidural morphine and intravenous ketamine. Statistics are the same as in figure 1. The two-factor mixed-design analysis of variance with repeated measurement on one factor and the Dunn test were used. *$P$ < 0.05, **$P$ < 0.005 *versus* the control group. ¶$P$ < 0.05, ¶¶$P$ < 0.005 *versus* the combination group. See table 1 for a definition of abbreviated terms.**

**Table 2. Categoric Pain Score**

| | Categoric Pain Score | | | | |
|---|---|---|---|---|---|
| Group | n = 3 | n = 2 | n = 1 | n = 0 | M (Q1, Q3) |
| MORep | 23 | 0 | 6 | 1 | 3 (2, 3) |
| KETiv | 17 | 1 | 8 | 3 | 3 (1, 3) |
| COMB | 4 | 1 | 10 | 16 | 0 (0, 1)* |
| CTL | 28 | 3 | 0 | 0 | 3 (3, 3) |

The Kruskal-Wallis test and Dunn test were used. Scores: 3 severe and using the PCA pump; 2 bearable and not using the PCA pump; 1 slight; 0 nil.

* $P$ < 0.005 versus the MORep, KETiv, and CTL groups (the Kruskal-Wallis test in combination with the Dunn test).

M = median; Q1 = first quartile; Q3 = third quartile; MORep = epidural morphine group; KETiv = intravenous ketamine group; COMB = combination group; CTL = control group.

ciceptive input and NMDA activation using epidural morphine and intravenous ketamine may be necessary for preemptive analgesia in gastrectomy. The sensitization mechanism in the spinal dorsal horn might be suppressed effectively by both treatments. This mechanism (dual blockade of opioid and NMDA receptors) may account for the current results.

In our recent study, however, epidural morphine alone exerted a definitively significant preemptive effect in patients undergoing orthopedic surgery without presurgical pain.[18] Some different preemptive effects observed in the current and previous studies may be attributable to differences in the surgical area (the upper abdomen and the extremity) and the surgical manipulation. These facts seem to indicate that pain perception during gastrectomy is regulated by multiple mechanisms.

The visceroperitoneal organs are innervated multiply by the spinal nerve (T5-T12),[14] the vagus nerve,[15,16] and the phrenic nerve (C3-C5)[14,17] in the upper abdomen. All these three nerves are associated closely with visceroperitoneal nociception. These facts suggest that central sensitization is induced not only segmentally but also heterosegmentally. In upper abdominal surgery, therefore, multiple blockades of afferent nociception may be necessary to attain definitive preemptive analgesia.

The effect of morphine was produced by segmental action on the spinal cord. Morphine exerts an analgesic effect at a lower dose if it is administered epidurally than if it is administered systemically, and the effective concentration is limited within the spinal cord.[23,24] Preemptive analgesia by epidural morphine appears to be produced mainly by action on the segmental spinal cord. Because epidural morphine has a dominant segmental analgesic effect, a minimum supra- or high-spinal effect appear to be another reason for the insufficiency in epidural preemptive analgesia. A study of preemptive analgesia in cholecystectomy supports our result: Effective preemptive treatment could be achieved by intraperitoneal local anesthesia[25] but not by cutaneous local anesthesia.[26]

Naloxone was administered after skin closure to block the continued effect of the preemptive morphine. Naloxone allows morphine to be released quickly from receptor sites. The free morphine diffuses out of the spinal cord into the whole body, where it is present at very low concentration and has little or no effect. Meanwhile, because of naloxone's transient effect,[27] epidural morphine administered postsurgically can be effective again. Intravenous naloxone was able to discontinue the effect of preemptive morphine without obstructing the effect of the postsurgical epidural morphine.

As shown in figure 1, the pain intensity in the combination group was very much lower at every time point observed than that in the control group, despite naloxone administration. Pain intensity in the epidural morphine group did not exceed that in the respective control groups. In other words, the intravenous naloxone administered after skin closure neither significantly increased postsurgical pain nor interfered with the action of the postsurgically administered morphine. This fact supports the use of naloxone for block of aftereffect of morphine.

Ketamine administered epidurally[20,28,29] and intrathecally[30,31] has been demonstrated to have insignificant analgesic or preemptive effect. Furthermore, analgesia by ketamine was not effective in decerebrated cats[32] nor in humans with supraspinal dysfunctions.[33-35] Based on these facts, the analgesic action site of ketamine is believed to be in the supraspinal structures. This may result from variation of displayed NMDA receptor subtypes,[36] and differential effects of ketamine[37] on different central nervous system sites. Because of the minimum spinal effect, the preemptive effect of intravenous low-dose ketamine was weak in this and previous studies.[21,22]

Of course, intravenous ketamine in a large dose may provide sufficient preemptive effect. One might suggest that the preemptive effect of high-dose ketamine should be examined. Intravenous high-dose ketamine may affect both the spinal cord and the brain stem. After anesthesia with high-dose ketamine, however, patients would sleep or be highly confused for a long time. Consequently, the VAS assessment would be impossible or could conceal postsurgical pain. For this reason, the effect of intravenous high-dose ketamine on preemptive analgesia was not tested in this study. The aftereffects of ketamine in this study appeared minimal because patients recovered awareness within 20 min after anesthesia, and consultation at 6 h was completed without problems.

The incomplete reduction of pain reported for the epidural morphine and intravenous low-dose ketamine groups appeared to be attributable not to the comparatively low dosage, but to a lack of effect on the heterosegmental supraspinal structure and the segmental spinal cord, respectively. Ilkjaer *et al.*[38] found that intravenous low-dose ketamine had no significant preemptive effect. This may be a result of the low dosage, in addition to the insufficient effect of intravenous ketamine.

In conclusion, definitive preemptive analgesia was achieved by the combination of epidural morphine and

intravenous ketamine in this study, suggesting blockade of noxious input and NMDA activation (dual blockade of opioid and NMDA receptors). The results also suggest that epidural morphine affects the spinal cord segmentally, and intravenous ketamine may block brain stem sensitization *via* the vagus or phrenic nerve during upper abdominal surgery. The complete blockade of nociceptive input and NMDA activation may be necessary for the definitive preemptive analgesic effect.

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