

# Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain

Ching-Yue Yang MD,\* Chih-Shung Wong MD PhD,\*  
Jang-Yang Chang MD,† Shung-Tai Ho MD\*

**Purpose:** Ketamine has been administered epidurally and intrathecally for operative and post-operative pain control. Animal studies showed potentiation of analgesia induced by ketamine and morphine. We hypothesized that intrathecal ketamine would potentiate the effects of intrathecal morphine in the treatment of cancer pain.

**Methods:** A double blind, cross over study was designed to evaluate the effect of ketamine on spinal morphine analgesia in terminal cancer pain patients. A two-phase protocol was used; phase M, intrathecal morphine alone twice daily; phase M+K, co-administration of ketamine (1.0 mg) with morphine intrathecally twice daily. The dose of morphine was titrated upwards until acceptable pain relief was achieved, defined by numeric rating scales (0–10)  $\leq 3$ , and the rescue dose of morphine was less than 5 mg after each intrathecal administration for two days. The dose of intrathecal morphine was defined as the effective dose.

**Results:** The effective dose of intrathecal morphine in phase M of  $0.38 \pm 0.04 \text{ mg} \cdot \text{day}^{-1}$  was higher than that in phase M+K

( $0.17 \pm 0.02 \text{ mg} \cdot \text{day}^{-1}$ ) ( $P < 0.05$ ). The average pain scales were  $7.95 \pm 0.25$  before intrathecal drug administration. Pain scales were decreased to  $2.2 \pm 0.17$  ( $P < 0.05$ ) in phase M and  $1.95 \pm 0.20$  ( $P < 0.05$ ) in phase M+K after the effective dose of morphine had been reached. No serious side effects were observed in this study.

**Conclusion:** The present study demonstrates that ketamine enhances the analgesic effect of morphine, thus reducing the dose of intrathecal morphine.

**Objectif:** La kétamine a été administrée par l'approche épidurale et sous-arachnoïdienne pour contrôler la douleur per- et postopératoire. Des études chez l'animal ont révélé que l'analgesie était potentialisée lorsque la kétamine était associée à la morphine. Nous avons vérifié si la kétamine sous-arachnoïdienne potentialisait la morphine sous-arachnoïdienne dans le traitement de la douleur du cancer.

**Méthodes:** Cette étude en double aveugle entrecroisée visait à évaluer l'effet de la kétamine sur la morphine sous-arachnoïdienne administrée à des cancéreux en phase terminale. Un protocole en deux phases a été élaboré pour la voie sous-arachnoïdienne: phase M, morphine seule deux fois par jour; phase M+K, association de kétamine (1,0 mg) avec morphine deux fois par jour. La dose de morphine a été augmentée jusqu'à ce qu'un niveau acceptable de soulagement soit atteint, défini sur une échelle numérique (0–10)  $\leq 3$ , et la dose de sauvetage de morphine a été inférieure à 5 mg après chaque administration sous-arachnoïdienne pour deux jours. La dose de morphine était définie comme la dose efficace.

**Résultats:** En phase M, la dose efficace de morphine sous-arachnoïdienne de  $0,38 \pm 0,04 \text{ mg} \cdot \text{j}^{-1}$  a été plus élevée qu'en phase M+K ( $0,17 \pm 0,02 \text{ mg} \cdot \text{j}^{-1}$ ) ( $P < 0,05$ ). Les échelles d'évaluation de la douleur moyenne étaient de  $7,95 \pm 0,25$  avant l'injection sous-arachnoïdienne. Ces échelles ont baissé à  $2,2 \pm 0,17$  ( $P < 0,05$ ) en phase M et à  $1,95 \pm 0,20$  ( $P < 0,05$ ) en phase M+K une fois la dose efficace de morphine atteinte. Il n'y a pas eu d'effets secondaires sérieux.

**Conclusion:** La présente étude montre que la kétamine augmente l'effet analgésique de la morphine et réduit ainsi la dose de morphine sous-arachnoïdienne.

## Key words

ANAESTHETIC TECHNIQUES: spinal;

ANALGESIA: cancer;

ANALGESICS: ketamine, morphine;

PAIN: cancer, chronic.

From the Department of Anesthesiology\* and Division of Hematology & Oncology†, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.

Address correspondence to: Dr. Ching-Yue Yang, Department of Anesthesiology, Tri-Service General Hospital, National Defense Medical Center, 8, Section 3, Ting-Chou Road, Taipei, Taiwan, 100, R.O.C.

Phone: 011-886-2-3659055-252. Fax: 011-886-2-3688781.

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TABLE I. Profile of patients

No	Sex	Age	Primary site	Location of pain	Duration (month)	Opioid usage
1	M	61	Stomach	Upper abdomen	30	<i>im</i> morphine
2	F	36	Cervix	Lower abdomen	6	<i>im</i> meperidine
3	F	57	Liver	Upper abdomen	3	<i>po</i> morphine
4	F	43	Liver	Upper abdomen	9	<i>im</i> meperidine
5	M	65	Lung	Right arm and shoulder	10	<i>iv</i> morphine
6	M	69	Lung	Lower back	12	<i>po</i> morphine
7	M	67	Liver	Upper abdomen	3	<i>im</i> meperidine
8	F	46	Stomach	Abdomen	10	<i>iv</i> morphine
9	M	55	Stomach	Upper abdomen	8	<i>im</i> morphine
10	M	62	Colon	Lower abdomen	24	<i>po</i> codeine <i>im</i> morphine
11	M	22	Liver	Upper abdomen	3	<i>im</i> meperidine
12	M	59	Lung	Right chest	36	<i>po</i> codeine
13	M	24	Lung	Lower back	7	<i>im</i> morphine
14	F	57	Cervix	Lower abdomen	36	<i>im</i> morphine
15	F	58	Colon	Lower abdomen and back	36	<i>po</i> morphine
16	F	38	Stomach	Abdomen	5	<i>im</i> meperidine
17	F	52	Pancreas	Upper abdomen	6	<i>iv</i> morphine
18	M	69	Colon	Back	18	<i>iv</i> morphine
19	F	68	Pancreas	Upper abdomen	6	<i>im</i> morphine
20	F	67	Stomach	Upper abdomen	7	<i>po</i> morphine

Spinal ketamine has been used for postoperative pain control and produces spinal anaesthesia after intrathecal administration.<sup>1-3</sup> Animal experiments showed that intrathecal administration of ketamine, with benzethonium chloride as preservative, was not associated with macroscopic abnormalities in the spinal cord.<sup>4,5</sup>

Intrathecal morphine has been used for cancer pain control, especially in patients who experience inadequate analgesia, intolerable side effects or who have an excellent response to intrathecal administration.<sup>6</sup> However, it is associated with many side effects, such as pruritus, nausea, vomiting, urinary retention, respiratory depression and tolerance.<sup>7</sup>

Animal studies have shown potentiation of analgesia by a combination of ketamine and morphine,<sup>8,9</sup> suggesting that ketamine involves opioid interaction. This study, in patients with terminal cancer pain, was designed to determine whether intrathecal ketamine potentiated in-trathecal morphine, and decreased its side effects.

## Methods

Twenty hospitalized patients, 10 men and 10 women, aged 22 to 69 yr were selected from patients referred to the Tri-service General Hospital, National Defense Medical Center from October 1993 to July 1995. The primary diagnosis included metastatic cervical cancer; lung cancer; hepatoma; colon cancer; pancreatic cancer and stomach cancer (Table I). The study was approved by the Ethics Committee of Health of the hospital, its

nature and purpose were described and written informed consent was obtained from each participant.

All patients used opioid analgesics for pain control before the study and the pain was of variable severity with pre-study analgesics. They all agreed to be implanted with an intrathecal Port-A-Cath (Pharmacia Deltec Inc. St Paul, MN 55112 U.S.A.), a catheter for intrathecal drug injection,<sup>10</sup> to control cancer pain. After implantation, the study was divided into two phases. In phase M (morphine), intrathecal morphine was given alone twice daily; and in phase M+K (morphine plus ketamine), ketamine 1.0 mg with benzethonium chloride as preservative was combined with morphine intrathecally twice daily. Intrathecal treatment began after random assignment to either phase M or phase M+K, with concomitant medications such as tranquilizers, bronchodilators or laxatives continued as previously. A double dummy technique was used, so that the patient, investigator and nurse were unaware of the dose of morphine and ketamine.

The intrathecal dose of morphine started at 0.05 mg and was increased in daily increments not exceeding the previous daily dose until acceptable analgesia was obtained (see below). The injected drug was flushed with 2 ml normal saline to ensure entrance into the intrathecal space (volume of reservoir and catheter of Port-A-Cath <0.7 ml).

A rescue dose of 5 mg morphine *im* was administered as needed for pain. Doses of intrathecal morphine were increased until acceptable analgesia or the effective dose

was achieved, i.e., rescue doses of morphine of  $\leq 5$  mg after each intrathecal administration and pain scale was  $\leq 3$ . After achieving and maintaining acceptable analgesia for 48 hr in the first phase of the study, patients were randomly crossed over to the alternate phase, again starting with intrathecal morphine titration. There was no washout period between two phases.

Self-assessment of pain, life interference and sleep deprivation were evaluated on a 0–10 numeric rating scale. Patients were asked to rate their pain from 0 (no pain at all) to 10 (the worst pain imaginable). Pain frequency was evaluated on a four point verbal ordinal scale (0, "none to rare"; 1, "occasional"; 2, "frequent"; or 3, "constant"). The intrathecal morphine dose, *im* rescue morphine dose and intrathecal morphine titrated frequency were also recorded. Side effects including pruritus, constipation, urinary retention, difficulty of urination, nausea, vomiting, hallucination and respiratory depression were evaluated by "yes" or "no". Respiratory depression was defined by a respiratory rate  $< 10$  per min. All evaluations were performed twice daily at the same time.

For statistical analysis, group differences in the effective dose of intrathecal morphine, total titrated dose of intrathecal morphine, total dose of *im* rescue morphine and total number of intrathecal injections between phase M and phase M+K were analyzed by paired t test. The difference in pain intensity, pain frequency, life interference and sleep deprivation were tested by repeated-measures ANOVA. Differences between groups were tested by Dunnett's test. The differences in the frequency of side effects between phase M and phase M+K were analyzed by repeated-measures chi-square test. Statistical significance was assessed when  $P < 0.05$ .

## Results

On the last day of phase M, patients required intrathecal morphine  $0.38 \pm 0.04$  mg  $\cdot$  day<sup>-1</sup> to obtain acceptable pain relief. On the last day of phase M+K, this had decreased to  $0.17 \pm 0.02$  mg  $\cdot$  day<sup>-1</sup> ( $P < 0.05$ ). The total titrated dose of intrathecal morphine, total dose of *im* rescue morphine and frequency of intrathecal morphine titration during phase M+K was less than in phase M ( $P < 0.05$ ) (Table II).

Pain intensity and frequency on the day before intrathecal morphine administration and on the last days of phase M and M+K are shown in Figure. 1. Pain intensity (numeric rating scale) and frequency (four point verbal ordinal scale) on the day before intrathecal administration were  $7.95 \pm 0.25$  and  $2.45 \pm 0.17$ , respectively, and these decreased to  $2.20 \pm 0.17$  ( $P < 0.05$ ) and  $0.35 \pm 0.11$  ( $P < 0.05$ ), respectively, on the last day of phase M and to  $1.95 \pm 0.20$  ( $P < 0.05$ ) and

TABLE II Intrathecal and rescue morphine requirements, and frequency of intrathecal morphine titration in Phase M and Phase M+K

	Phase M	Phase M+K
Effective dose of intrathecal morphine (mg)	$0.38 \pm 0.04$	$0.17 \pm 0.02^*$
Total dose of intrathecal morphine during treatment (mg)	$1.32 \pm 0.19$	$0.38 \pm 0.08^*$
Total dose of rescue morphine during treatment (mg)	$33.25 \pm 7.40$	$9.00 \pm 3.58^*$
Frequency of intrathecal morphine titration	$9.10 \pm 0.51$	$5.00 \pm 0.40^*$

Value are mean  $\pm$  SEM,  $n = 20$ .

Phase M, intrathecal morphine only; phase M+K, co-administered ketamine 1 mg with morphine.

\* $P < 0.05$  vs Phase M.

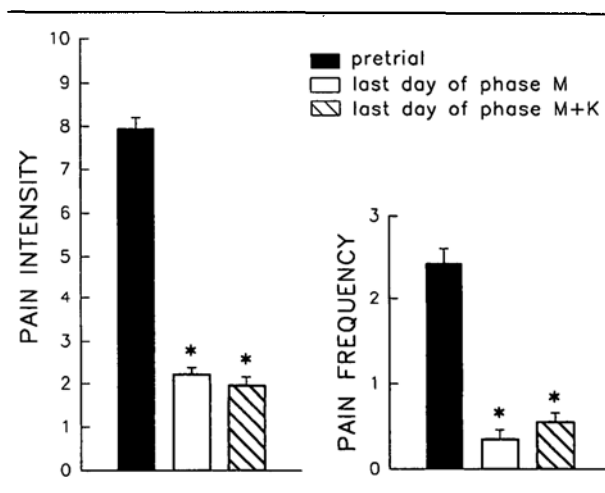


FIGURE 1 Pain intensity (numeric rating scale) and frequency (four point verbal ordinal scale) on the day before intrathecal administration and on the last day of the two phases. Value are mean  $\pm$  SEM,  $n = 20$ . Phase M, intrathecal morphine only; phase M+K, co-administered ketamine 1 mg with morphine. \* $P < 0.05$  vs before intrathecal administration.

$0.55 \pm 0.11$  ( $P < 0.05$ ), respectively, on the last day of phase M+K.

Most of the patients had life interference and sleep deprivation before intrathecal administration, with scales (numeric rating scale) averaging  $7.60 \pm 0.29$  and  $7.45 \pm 0.29$ , respectively. These improved after intrathecal drug administration to  $2.25 \pm 0.25$  ( $P < 0.05$ ) and  $2.00 \pm 0.63$  ( $P < 0.05$ ) on the last day of phase M,  $2.05 \pm 0.25$  ( $P < 0.05$ ) and  $1.65 \pm 0.48$  ( $P < 0.05$ ) on the last day of phase M+K (Figure. 2).

Side effects including pruritus, constipation, urinary retention, difficulty of urination, nausea, vomiting and hallucination, were not serious and respiratory depression did not occur (Table III).

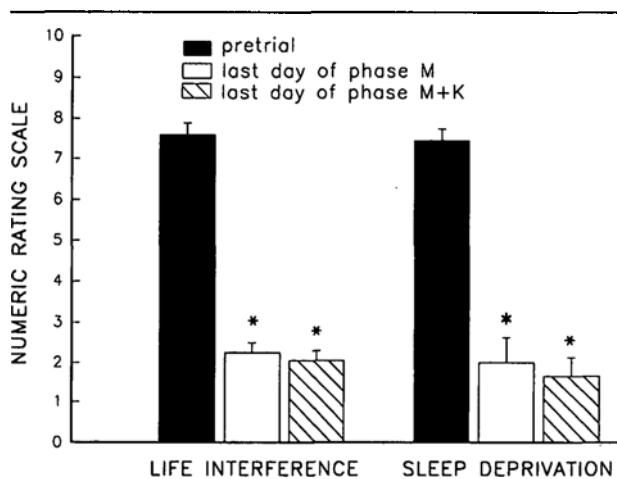


FIGURE 2 Life interference and sleep deprivation on the day before intrathecal administration and on the last day of the two phases. Value are mean  $\pm$  SEM,  $n = 20$ . Phase M, intrathecal morphine only; phase M+K, co-administered ketamine 1 mg with morphine. \* $P < 0.05$  vs before intrathecal administration.

TABLE III Frequency and incidence of side effects ( $n = 20$ ).

Side effects	Pretrial	Phase I	Phase II
Pruritus	0(0%)	5(25%)	3(15%)
Constipation	4(20%)	5(25%)	4(20%)
Urinary retention	2(10%)	4(20%)	2(10%)
Difficult urination	2(10%)	7(35%)	7(35%)
Nausea	6(30%)	8(40%)	6(30%)
Vomiting	5(25%)	6(30%)	4(20%)
Hallucinations	0(0%)	1(5%)	0(0%)
Respiratory depression	0(0%)	0(0%)	0(0%)

Five patients experienced pruritus during phase M, and three during phase M+K. Four patients were constipated before intrathecal administration and during phase M+K, and one additional patient experienced constipation during phase M. Difficulty in voiding was a major side effect. Two patients needed bladder catheterization before intrathecal drug administration, and a further two patients developed urinary retention during phase M. Five patients experienced difficulty of urination after intrathecal drug administration during phases M and M+K. Six patients experienced nausea before intrathecal drug administration and during phase M and M+K, and two additional patients experienced nausea only during phase M. Five patients experienced vomiting before intrathecal drug treatment; one additional patient experienced it during phase M, but only four patients vomited during phase M+K. One patient had hallucinations during phase M, but these improved during phase M+K. The frequency of these side effects did not show differences between phase M and phase M+K ( $P > 0.05$ ).

## Discussion

The present study showed pain intensity, frequency, life interference and sleep deprivation were all decreased on the last days of phases M and M+K. Intrathecal morphine alone or the co-administration of morphine with ketamine intrathecally can control cancer pain and improve the life and sleep of patients. The dose of intrathecal morphine on the last day of phase M+K was less than that on the last day of phase M, suggesting that co-administration of morphine with small dose of ketamine (1 mg) intrathecally reduces the intrathecal dose of morphine required for the control of cancer pain, and is as effective as intrathecal morphine alone. Recently, animal experiments have shown that systemic administration of NMDA receptor antagonists attenuates non-associative opioid tolerance.<sup>11-13</sup> Gustein *et al.*<sup>14</sup> demonstrated that non-competitive NMDA receptor antagonist, MK-801, prevents the development of morphine tolerance at spinal sites of rats. Furthermore, we demonstrated that co-administration of MK-801 with morphine intrathecally inhibits the development of morphine tolerance in rats.<sup>15</sup> Ketamine, a non-competitive NMDA antagonist, interacts with morphine and potentiates the action of morphine in rats.<sup>8,9</sup> Trujillo *et al.*<sup>13</sup> further demonstrated that ketamine inhibits opioid tolerance in rats. In human investigations, ketamine has been used for post-operative pain relief. Islas *et al.*<sup>3</sup> found that epidural ketamine produced postoperative pain relief without opioid-induced side effects. Laird *et al.*<sup>16</sup> and Clark *et al.*<sup>17</sup> reported that ketamine might reverse morphine tolerance in two patients with severe cancer pain. Recently, we demonstrated that epidural ketamine potentiates the analgesic effect of morphine in patients undergoing total knee replacement.<sup>18</sup> The present findings support results from studies in animals and humans, indicating that there is an interaction between ketamine and morphine: ketamine potentiates the analgesic action of morphine.<sup>8,9,13,16-18</sup>

From the beginning of intrathecal morphine titration, the total intrathecal titrated dose, total *im* rescue dose and intrathecal titrated frequency of morphine during phase M+K to achieve acceptable pain relief was less than in phase M, suggesting that the concomitant use of intrathecal ketamine and morphine is more convenient for morphine's titration and adjustment than intrathecal morphine alone.

Side effects in this study included pruritus, constipation, urinary retention, difficult urination, nausea, vomiting and hallucination. Pruritus was the most common adverse effect of intrathecal drugs but its mechanism is still unknown.<sup>7</sup> Difficulty in urination was also common and occurred only in men. Urinary retention was the most troublesome complication.<sup>7,19</sup> It did not occur fre-

quently, but only in two additional patients during phase M. Nausea, vomiting, and constipation were seen but most of these symptoms existed before intrathecal drug treatment started. One patient developed hallucinations during phase M, and he had required a larger dose of morphine to relieve his pain. Hallucinations disappeared when the morphine dose was reduced during phase M+K. There were no serious side effects in this study such as life-threatening respiratory depression,<sup>20,21</sup> perhaps because the dose of intrathecal morphine was adjusted by titration and overdose was avoided. Although the incidence of some side effects numerically was lower in the M+K group than in group M, the difference was not statistically significant, probably because of the small number of patients and brief trial period.

In conclusion, co-administration of intrathecal morphine with a small dose of ketamine (1 mg) reduces the intrathecal dose of morphine required to control cancer mediated pain and is as effective as intrathecal morphine alone. The concomitant use of intrathecal morphine and ketamine appeared to enable easier adjustment of the dose of intrathecal morphine than intrathecal morphine alone. There were no serious side effects. Thus, the concomitant use of intrathecal morphine and ketamine is an effective and safe method of cancer pain control.

#### Acknowledgements

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