Original Article

Efficacy of a Combination of Ketamine and Morphine for Intravenous Patient Controlled-Analgesia in Upper Abdominal Surgery: A Prospective, Double-blind, Randomized Controlled Trial

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Background: Most postoperative upper abdominal pain is severe, and various methods can be employed to control it. Presently, morphine is the main drug used for anesthesia, but it may contribute to the occurrence of many uncomfortable side effects. Ketamine is an analgesic drug that inhibits NMDA receptors, making it a synergistic effect of morphine.

Objective: To investigate the efficacy of a combination of ketamine and morphine in controlling postoperative upper abdominal pain.

Materials and Methods: Informed consents were obtained from patients enrolled into the present double-blind randomized study that divided into two groups, (i) the M group, which received 1 mg/mL of morphine, and (ii) the MK group, which received 1 mg of ketamine plus 1 mg/mL of morphine as intravenous patient-controlled analgesia (IV-PCA) post-operation. All patients were assessed based on postoperative morphine consumption, a numeric rating scale (NRS) used to rate pain, and the presence of side effects.

Results: Sixty-seven patients completed the study including 34 patients in the MK group and 33 patients in the M group. Cumulative postoperative morphine consumption at 24 and 48 hours was significantly lower in the MK group at 27.91±11.11 and 46.44±15.21 mg compared to the M group at 43.24±15.32 and 71.33±19.67 mg, respectively ($p<0.001$). NRS were similar between the two groups and no observable differences regarding to side effects.

Conclusion: A combination of ketamine and morphine via IV PCA is effective in controlling postoperative upper abdominal pain.

Keywords: Ketamine; Morphine; Upper abdominal surgery; Intravenous patient-controlled analgesia

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Upper abdominal surgery can lead to severe postoperative abdominal pain[1]. Inadequate control of this pain can result in patients' discomfort, shallow breathing, retention of secretions, atelectasis, and lack of cooperation in physiotherapy, which increase the incidence of post-operative morbidity and delayed recovery[2].

There are many methods employed to control pain. Epidural analgesia remains a key component of anesthesia-based acute pain service and is often used to treat acute pain after abdominal surgery[3]. However, this method often results in failure of techniques and is sometimes contraindicated or refused by patients. Morphine is the most common analgesic drug, but it also has many uncomfortable side effects, such as nausea, vomiting, sedation, and respiratory depression[4].

Intravenous patient-controlled analgesia (IV-PCA) has been proposed as a safe and effective technique for postoperative analgesia[5]. Pain-control levels can be more effectively adjusted using IV-PCA than a bolus dose, limiting the adverse effects of the opioids and increasing patient satisfaction and cooperation[6]. Ketamine, a non-competitive NMDA receptor antagonist, is an adjuvant intravenous analgesic drug that could be used to reduce morphine consumption and morphine-related side effects[4]. Sub-anesthetic doses of ketamine have also been used as an analgesic for both acute and chronic pain relief[7].

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A combination of ketamine and morphine administered via IV-PCA has been shown to decrease both postoperative pain and morphine consumption in cases involving several types of orthopedic and thoracic surgeries[4,8-12]. In addition, some studies have reported potential benefits of continuous ketamine infusion after abdominal surgery[13-16]. However, few studies have confirmed the existence of any significant benefits of a combination of ketamine and morphine via IV-PCA on upper abdominal surgeries. The authors hypothesized that combination of low-dose ketamine and morphine via IV-PCA could effectively reduce postoperative morphine consumption, pain, and adverse effects.

Materials and Methods

Design and setting

The present study was a prospective, double-blind, randomized controlled trial, approved by Khon Kaen University Ethics Committee in Human Research based on the declaration of Helsinki and ICH good clinical guidelines, reference No. HE571441. The study was also registered at the Thai Clinical Trials Registry (TCTR), registration number TCTR20210708002. Patients undergoing elective upper abdominal surgery at Srinagarind Hospital between January and August 2015 were randomized using a computer-generated block of four to allocate the subjects into two groups, which (i) the M group received 1 mg/mL of morphine, and (ii) the MK group received 1 mg of ketamine plus 1 mg/mL of morphine via IV-PCA. Allocation concealment was performed using opaque, sealed envelopes. Patients and investigators were blinded to the treatment assignments. Informed consent was obtained from each patient.

Patients 18 to 65 years of age, classified as the American Society of Anesthesiologists (ASA) physical status class I to II were eligible for enrollment to the present study. Patients who had a history of chronic opioid use, history of chronic pain, undergone a neuraxial block, allergies to morphine or ketamine, suffered from psychiatric disorders, or being unable to operate the IV-PCA were excluded from the study.

Procedure

One day before surgery, patients were instructed on how to use the PCA device for postoperative analgesia, and they assessed their pain by using a numeric rating scale (NRS), both at rest and during movement. All patients received standard anesthetic care from an anesthesiologist blinded to the drug assignment. General anesthesia consisted of 0.1 mg/kg of morphine and 2 mg/kg of propofol induced intravenously facilitated by endotracheal intubation with 0.15 mg/kg of cisatracurium. Anesthesia was maintained with 2% expired sevoflurane concentration, a combination of oxygen and air to preserve a fractional inspired oxygen concentration of 0.4 to 0.6, and repeated doses of morphine and cisatracurium when deemed necessary. During the intraoperative period, no non-steroidal anti-inflammatory drugs (NSAIDs) or analgesic medications were given. After surgery, neuromuscular blocking was reversed using 0.02 mg/kg of atropine and 0.05 mg/kg of neostigmine administered intravenously. The endotracheal tube was then removed, followed by extubation criteria. An IV-PCA pump set to 1 mL per dose with a lockout time of five minutes and limited to 8 mL per hour with no continuous infusion was connected at the end of surgery before patients were transferred to the post-anesthetic care unit (PACU). At the PACU all patients received 2 mg of morphine via intravenous bolus titrate every five minutes until their NRS was less than five. Then, they began an IV-PCA regimen that continued for 48 hours. Patients received standard PACU care by anesthetist nurses blinded to the drug assignment.

Demographic data such as age, gender, weight, ASA physical status, type of incision, type of operation, intraoperative morphine use, and duration of surgery were recorded. Cumulative morphine IV-PCA use at 24 and at 48 hours' post-operation were recorded. NRS of pain at rest and during movement, and side effects were evaluated 1-hour post-operation (T1) at the PACU by nurse anesthetists and then at 4-, 12-, 24-, 36-, and 48-hours post-operation (T4, T12, T24, T36, and T48, respectively) by ward nurses blinded to the drug assignment.

Outcomes

The primary outcome examined in the present study was cumulative morphine consumption during the 48 hours' post-operation. Secondary outcomes were pain NRS and side effects such as sedative scores, postoperative nausea, and vomiting (PONV), urinary retention, pruritus, hallucinations, and nightmares.

Statistical analysis

The required sample size was calculated to detect a 30% difference in morphine consumption between the two groups with an α of 0.05, power of 0.90 and dropout rate of 20%. The assumed mean

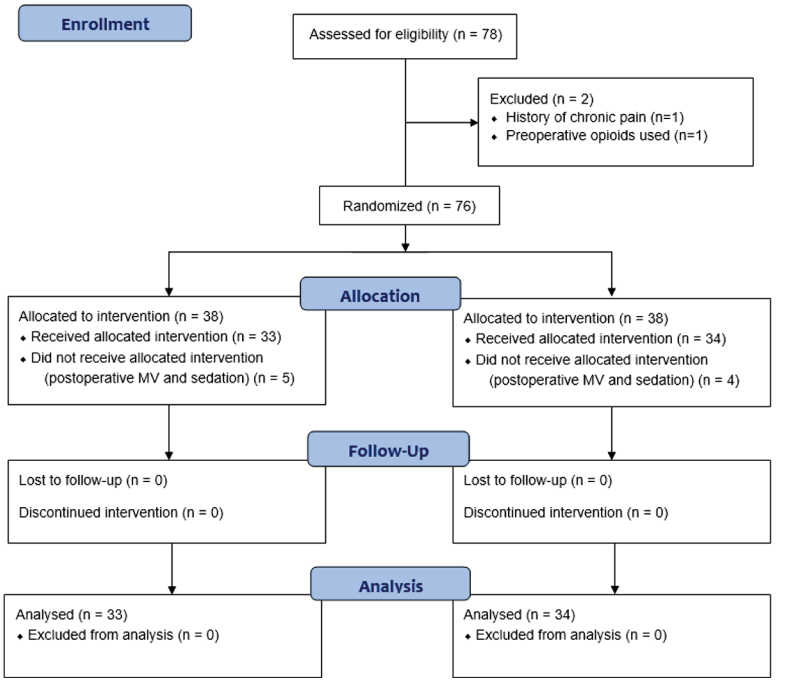

Figure 1. Study flow diagram showing patient selection and randomization.

MV=mechanical ventilator

amount of morphine consumption was 50±21 mg, based on a previous study[15]. As a result, it needed to be a minimum of 31 patients in each group. Data were analyzed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). Results were presented as a mean ± standard deviation or median (interquartile range) for quantitative variables, and as a number or percentage for qualitative variables. An independent samples t-test or Mann-Whitney U test was used for analysis continuous data and chi-square test, or Fisher's exact test was applied to categorical data. A two-way repeated measures ANOVA followed by a Tukey's post hoc test was used to evaluate the effects of time and IV-PCA regimen on pain NRS. A p-value of less than 0.05 was considered statistically significant.

Results

Seventy-eight patients fulfilled the enrollment criteria for the present study. Two patients were excluded due to history of chronic pain and having had used preoperative opioids. Nine patients dropped out of the study after surgery because they required postoperative ventilation support and sedation. Therefore, 67 patients completed the study with 33 in the M group and 34 in the MK group (Figure 1). Baseline characteristic and intraoperative data were similar between the two groups, except with regard to intraoperative morphine consumption, which was significantly lower in the MK group (Table 1).

In terms of the primary outcome, there was a significant reduction in cumulative morphine consumption in the MK group compared to the M group at all periods until 48 hours' post-operation, as shown in Table 2. There was no difference in self-reported pain NRS, either at rest or during movement between the groups for 48 hours after surgery as shown in Figure 2 and 3, respectively.

The main side effects of morphine and ketamine are shown in Table 3. There were no differences regarding to sedation scores, PONV, urinary retention, or pruritus between the two groups. One patient in the MK group suffered from hallucinations, but no statistical significance. There was no incidence of nightmares.

Discussion

Nociceptive stimulation produces hyper-excitability by activation of the NMDA receptors, a process involved in the pathophysiology of acute pain[17]. Ketamine, a non-competitive NMDA receptor antagonist can prevent the induction of central

Table 1. Baseline characteristics and intraoperative data of the patients

Variables	M group (n=33); n (%)	MK group (n=34); n (%)	p-value
Sex			0.167
Male	22 (66.7)	17 (50.0)	
Female	11 (33.3)	17 (50.0)	
Age (years); mean±SD	53.9±15.5	56.3±10.3	0.364
Body weight (kg); mean±SD	61.8±15.5	58.79±14.0	0.299
ASA physical status			0.223
Class I	4 (12.1)	8 (23.5)	
Class II	29 (87.9)	26 (76.5)	
Type of incision			0.417
Midline	14 (42.4)	15 (44.1)	
Subcostal	6 (18.2)	10 (29.4)	
Mirror L	13 (39.4)	9 (26.5)	
Type of operation			0.962
Hepatobiliary	19 (57.6)	16 (47.0)	
Gastrointestinal	9 (27.3)	11 (32.4)	
Other	5 (15.1)	7 (20.6)	
Intraoperative morphine (mg); mean±SD	16.6±8.0	13.1±6.9	0.018
Duration of surgery (minutes); mean±SD	181.5±115.4	181.5±116.2	1.000

ASA=American Society of Anesthesiology; SD=standard deviation

Table 2. Cumulative postoperative morphine consumption between the groups

Variables	M group (n=33); mean±SD	MK group (n=34); mean±SD	Mean difference (95% CI)	p-value
Cumulative morphine consumption (mg)				
24 hours postoperative	43.24±15.32	27.91±11.11	15.33 (8.82 to 21.85)	<0.001*
48 hours postoperative	71.33±19.67	46.44±15.21	24.89 (16.28 to 33.50)	<0.001*

SD=standard deviation; NRS=numeric rating scale

* p<0.05 is statistically significant

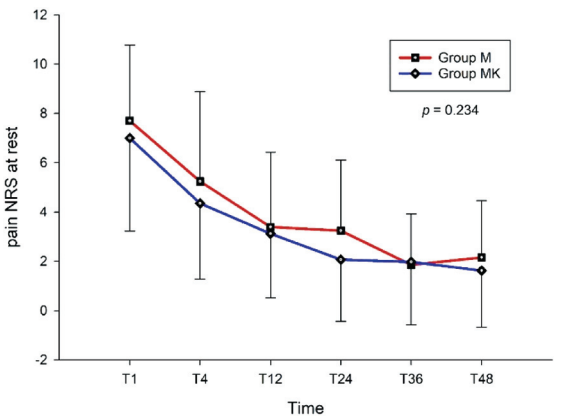

Figure 2. Pain NRS at rest between groups.

Data are expressed as means (SD) (p=0.234 by ANOVA)

NRS=numeric rating scale; T=post-operative time

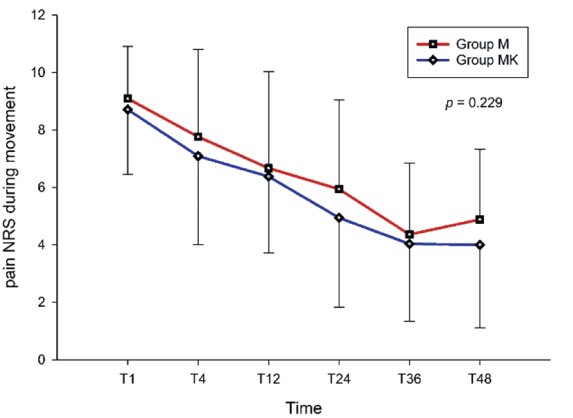

Figure 3. Pain NRS during movement between groups.

Data are expressed as means (SD) (p=0.229 by ANOVA)

NRS=numeric rating scale; T=post-operative time

Table 3. Main side effects of morphine and ketamine within 48 hours of patients between the groups

Variables	M group (n=33); n (%)	MK group (n=34); n (%)	p-value
Sedation score at 24 hours			0.895
0	20 (60.6)	22 (64.7)	
1	10 (30.3)	9 (26.5)	
2	2 (6.1)	3 (8.8)	
3	1 (3.0)	0 (0.0)	
Sedation score at 48 hours			0.548
0	30 (90.9)	31 (91.2)	
1	3 (9.1)	2 (5.9)	
2	0 (0.0)	1 (2.9)	
3	0 (0.0)	0 (0.0)	
Severity of PONV at 24 hours			0.084
0	27 (81.8)	33 (97.1)	
1	2 (6.1)	0 (0.0)	
2	4 (12.1)	1 (2.9)	
3	0 (0.0)	0 (0.0)	
Severity of PONV at 48 hours			0.611
0	32 (97.0)	32 (94.2)	
1	1 (3.0)	1 (2.9)	
2	0 (0.0)	1 (2.9)	
3	0 (0.0)	0 (0.0)	
Urinary retention			0.306
Yes	1 (3.0)	0 (0.0)	
Retained FC	32 (97.0)	34 (100)	
Pruritus	4 (12.1)	1 (2.9)	0.153
Hallucinations	0 (0.0)	1 (2.9)	0.321
Nightmares	0 (0.0)	0 (0.0)	N/A

PONV=postoperative nausea and vomiting; FC=Foley catheter

Sedation score: 0=alert, 1=occasional drowsy, 2=constantly drowsy but easy to arouse, 3=somnolent and difficult to arouse; Severity of PONV: 0=no symptoms, 1=mild symptoms (do not require treatment), 2=moderate symptoms and require treatment, 3=not improved after treatment

* $p<0.05$ is statistically significant

sensitization caused by stimulation of peripheral nociception[18]. Furthermore, administration of an NMDA antagonist and opioids may result in a synergistic effect[19]. In the present study, ketamine was used during the postoperative period. Although there have been various combinations of ketamine and morphine IV-PCA dose regimens used in the previous studies, a 1:1 morphine:ketamine ratio has been the most common[6]. However, the optimal dosage remains controversial. The present study used 1 mg of morphine plus 1 mg of ketamine per 1 mL of IV-PCA.

Randomized controlled studies comparing a combination of ketamine and morphine with morphine alone via IV-PCA have been conducted using several types of surgeries such as microdiscectomy[4], orthopedic-oncologic surgery[8], thoracic surgery[9,10], and minimally invasive direct coronary artery bypass surgery[11,12]. In all these studies, the ketamine groups have had lower pain scores and 25% to 55% decreases in morphine consumption during the postoperative period. These results are similar to the present study, in which ketamine was shown to have a 31.2% morphine-sparing effect. Other studies have similarly shown intravenous ketamine infusion to decrease postoperative morphine consumption in cases of major abdominal surgery[13-16].

Reeves et al[20], however, found that IV-PCA consisting of a combination of ketamine and morphine at a 1:1 ratio did not lead to any difference in morphine consumption after major abdominal surgery. This was because most of the patients in that study underwent gastrointestinal surgery (44%), which contributes to abdominal colic, a type of discomfort not relieved by NMDA antagonists. Unlugenc et al[21] used 0.4 mg of morphine plus 1 mg of ketamine per 1 mL of IV-PCA solution compared with 0.4 mg of morphine alone per 1 mL and found only a 5% morphine reduction in the ketamine group. This may be because 0.4 mg morphine is too low of a concentration. In addition, that study used a 20-minute lockout time, which may have been too long to facilitate adequate pain relief. Imani et al[22] administered ketamine and fentanyl via IV-PCA and found no difference in postoperative pain scores after abdominal surgery. He believed that adding ketamine to fentanyl should raise patients pain thresholds.

The present study demonstrated that a combination of low-dose ketamine and morphine delivered via IV-PCA for postoperative pain relief resulted in lower morphine consumption during the 48 hours after upper abdominal surgery compared with morphine alone. In addition, the MK group showed similar levels of pain reduction and no increase in side effects compared to the M group.

In the present study, patient demographic characteristics and intraoperative data were similar between the two groups, with the exception of intra-operative morphine use, which was lower in the MK group at 13.06 mg compared to the M group at 16.57 mg. This is because anesthesiologists had to adjust the morphine requirement during anesthesia for each case due to uncontrolled differences. Despite more intra-operative morphine being used in the M group, however, postoperative morphine consumption was

higher.

Postoperative pain NRS levels were similar in both groups despite there being significantly less morphine consumption in the MK group, a result that differs from those of the previous studies[4,8-12], less morphine consumption with lower pain intensity in MK group. However, this is not surprising, as patients were able to receive repeated doses of analgesic solution via IV-PCA, which allowed them to reduce their pain levels until they were comfortable, leading to similar pain scores in both groups. The initial pain levels, both at rest and during movement at the PACU were high at 7.3 to 8.3 in the M group and 7.2 to 8.2 in the MK group, which is assumed to have been due to inadequate intraoperative pain management. It is, thus, recommended that the anesthesiologist should apply the multimodal strategy to make improvement in perioperative pain control.

Although, the authors expected that a reduction in postoperative morphine used would lead to decreased side effects, the present study results did not show any difference with regard to side effects between the two groups. This result conflicts with those of some previous studies, which had shown lower incidence rates of side effects, such as vomiting, after several types of surgery in patients given ketamine due to decreased morphine consumption[4,8,9,13]. Javery et al[4], for example, reported that a 49.47% reduction in morphine use in patients given a combination of ketamine and morphine via IV-PCA after they underwent microdiscectomy led to a lower incidence of urinary retention, nausea, vomiting, and pruritus. The present study results show no difference with regard to side effects due to lower rates of morphine consumption at 31.2%. In the present study, all patients retained Foley catheters during the postoperative period for more than two days, making it difficult to evaluate difference in urinary retention between the two groups. One patient suffered from hallucinations in the MK group, but this was not statistically significant. There were no nightmares reported, as only very small self-limited doses of ketamine were administered.

The present study design had several limitations. Different anesthesiologists may have conducted intraoperative management differently, leading to variations in intraoperative data. In addition, the short duration of the follow-up period, which was 48 hours, cannot account for chronic pain and long-term patient satisfaction. Another limitation was that variations regarding skin incisions and types of surgeries may lead to differences in pain levels. However, these factors were similar in both groups.

Conclusion

A combination of low-dose ketamine and morphine administered via IV-PCA at a 1:1 ratio decreased morphine consumption, provided equivalent analgesia, and were equally safe for patients undergoing upper abdominal surgery. Further studies should be aimed at finding the optimal dosage or ratio of ketamine and morphine for an IV-PCA regimen in cases of upper abdominal surgery and should include hemodynamic and respiratory profiles in their results.

What is already known on this topic?

Ketamine has a role in acute postoperative pain management by reducing the amount of opioids required. A combination of ketamine and morphine administered via IV-PCA has been shown to decrease both postoperative pain and morphine consumption in orthopedic and thoracic surgeries[4,8-12].

What this study adds?

This study confirmed the benefits of a combination of ketamine and morphine via IV-PCA on upper abdominal surgeries for pain management without a neuraxial block.

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Conflicts of interest

The authors declare no conflict of interest.

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