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Prospective Randomized Trial of Patient-Controlled Analgesia with Ketamine and Morphine or Morphine Alone after Hysterectomy

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ABSTRACT

Background: Previous studies have shown that adding ketamine to morphine for postsurgical pain can reduce the unwanted side effects of morphine. However, it is not known if the combination of ketamine and morphine reduces pain to a greater extent than morphine alone after hysterectomy.

Objective: The primary objective was to determine whether the use of low-dose ketamine with morphine reduces pain to a greater extent than morphine alone. The secondary objective was to determine whether the use of low-dose ketamine with morphine was associated with fewer unwanted adverse effects.

Methods: Thirty women scheduled for abdominal hysterectomy were randomly assigned to receive either ketamine and morphine or morphine alone. A double-blind procedure was used. Pharmacy staff prepared the syringes for patient-controlled analgesia, using a 1:1 ratio of 2 mg/mL solutions for the combination treatment and a solution with concentration 2 mg/mL for the morphine-only treatment. The Mann–Whitney *U* test was used to compare identified outcome measures for the 2 groups (nausea and vomiting, sedation, dizziness, hallucinations, nightmares, dreams, and amount of drug consumed).

Results: There were no significant differences between the 2 treatment groups for the primary outcome of pain after 24 h or for any of the secondary outcome measures.

Conclusions: This study adds to the body of knowledge indicating that low-dose ketamine and morphine combined is no better than morphine alone in alleviating pain and that the combination offers no advantage in terms of unwanted side effects.

Key words: pain, randomized study, ketamine, morphine

RÉSUMÉ

Contexte : Des études ont montré que l'ajout de kétamine à la morphine pour le contrôle de la douleur postchirurgicale peut réduire les effets secondaires indésirables de la morphine. En revanche, on ignore si l'ajout de kétamine à la morphine soulage la douleur dans une plus large mesure que l'emploi de la morphine seule après une hystérectomie.

Objectif : L'objectif primaire était de déterminer si l'emploi de kétamine à faible dose avec la morphine soulageait la douleur davantage que la morphine employée seule. L'objectif secondaire était de déterminer si l'emploi de kétamine à faible dose avec la morphine réduisait les effets secondaires indésirables de la morphine.

Méthode : Dans le cadre de cette étude à double insu, trente femmes devant subir une hystérectomie par voie abdominale ont été réparties au hasard pour recevoir soit l'association kétamine-morphine, soit la morphine seule. Le personnel de la pharmacie a préparé les seringues pour l'analgésie contrôlée par le patient : l'association kétamine-morphine dans un rapport 1:1 de solutions de 2 mg/mL, et la morphine employée seule à une concentration de 2 mg/mL. Le test U de Mann–Whitney a été utilisé pour comparer les résultats obtenus dans les deux groupes.

Résultats : On n'a observé aucune différence significative entre les deux groupes pour ce qui est du paramètre d'évaluation primaire de la douleur après 24 heures, ni pour ce qui est des paramètres d'évaluation secondaires (vertige, nausée et vomissement, sédation, hallucination, cauchemar, rêve et quantité de médicaments consommée).

Conclusions : Cette étude vient étayer davantage les données à l'effet que l'association de kétamine à faible dose et de morphine n'est pas supérieure à la morphine employée seule pour soulager la douleur et n'offre aucun avantage en termes de réduction d'effets secondaires indésirables.

Mots clés : douleur, étude à répartition aléatoire, kétamine, morphine

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INTRODUCTION

Morphine is commonly used as an analgesic for the control of postoperative pain and is the "gold standard" against which all other analgesics are compared. Morphine acts mainly as an agonist at specific receptor sites in the central nervous system. Evidence suggests that both hyperanalgesic effects after tissue injury and opioid tolerance involve activation of the *N*-methyl-D-aspartate (NMDA) receptor and subsequent biochemical processes that result in central sensitization.[1] Morphine also causes many undesirable side effects, including nausea and vomiting through direct stimulation of the chemoreceptor trigger zone.[2]

Ketamine, an NMDA receptor antagonist, has both analgesic and anesthetic effects. The mechanisms by which it enhances analgesic effects probably occur within the dorsal horn of the spinal cord. The dorsal horn neuron has both μ-opioid and NMDA-receptors.[3] Ketamine blocks the NMDA receptors, reducing central sensitization, while also producing opioid-sparing effects. At normal anesthetic doses, ketamine produces undesirable psychotomimetic effects (dizziness, hallucinations, and dreams),[4] but lower doses are postulated to generate fewer side effects. The addition of low-dose ketamine to morphine for patient-controlled analgesia (PCA) is not a novel idea and has been studied by other researchers. In 1996, Javery and others[5] suggested that low-dose ketamine added to morphine might yield a morphine-sparing effect without psychotomimetic effects. Their research sparked interest in using an old drug in a new way; however, that study was limited to patients undergoing microdiskectomy, a rare surgical procedure. Those authors used PCA to deliver the opioid agents, a method that has gained prominence in the surgical field. This technique allows patients to self-administer preset amounts of drugs by a syringe pump that interfaces electronically with a timing device. Using this technique, the patients can balance pain control with sedation.[6]

Abdominal hysterectomy is commonly performed at the authors' institution. Because of postoperative pain, patients who have undergone this procedure usually require large doses of opioids,[7] and the drugs are commonly administered by PCA.

The data for the study reported here were collected in 2001. To check whether other similar studies had been done in the interim, we updated our literature search for the period 2002 to 2007 and found 2 studies involving the combination of ketamine and morphine. In 2004, Subramaniam and others[7] concluded that low-dose ketamine was a safe and useful adjuvant to standard opioid analgesia. In the same year, Schulte and others[8] reported that the combination of low-dose ketamine and morphine led to synergistic analgesic effects. Although both groups of researchers reported positive outcomes and a synergistic effect when ketamine was added to morphine, we felt that publishing the findings of our own study would still be relevant, as these results provide valuable information for a specific group of patients (women undergoing hysterectomy).

The purpose of this prospective double-blind, randomized study was to examine whether the combination of low-dose ketamine and morphine (in a 1:1 ratio) delivered by PCA would be associated with superior analgesic efficacy (i.e., less pain) than morphine alone, also delivered by PCA. In addition, the outcomes of nausea and vomiting, sedation, dizziness, hallucinations, nightmares, dreams, and lower drug usage were compared between the 2 treatment groups.

PATIENTS AND METHODS

The Pharmacy and Therapeutics Committee at the authors' institution reviewed the protocol for this study, and approval was obtained from the Research Ethics Board. The study began in July 2001, and the original goal was to recruit 50 patients. However, in July 2002 the study was interrupted by a labour disruption and was never resumed.

All women 21 years of age or older who were scheduled for abdominal hysterectomy during the study period and who met the inclusion and exclusion criteria (Appendix 1) were informed of the study, and all agreed to participate. During an interview at the preadmission clinic, a pharmacist (A.L.) informed each patient about the risks and benefits of the study and provided instructions on how to use the PCA device.

Randomization was accomplished manually using a sealed-envelope system; unique numbers enclosed in the envelopes were used to generate the 2 groups, as described below. Of the original total of 50 envelopes prepared, 30 were distributed, 15 for each of the 2 treatment groups. Each patient was asked to select an envelope, and the enclosed number was used to assign the patient to receive either ketamine and morphine or morphine alone. Ketamine has been added to morphine in previous studies, but there were no defined dosages for this combination. Therefore, the combination treatment consisted of a 1:1 mixture of ketamine 2 mg/mL and morphine 2 mg/mL; the morphine-only treatment consisted of a 2 mg/mL solution. Body mass index was calculated to account for any difference in volume of

distribution for patients who received both morphine and ketamine. The concentrations chosen were different from those used in other similar studies. The treatments were to be delivered as postoperative PCA, via syringes prepared by pharmacy technicians. There was no wash-out period, no placebo group, no additional investigation or invasive procedures, and no permanent implantation of devices. Neither the patients nor the investigators were aware of the groups to which patients had been assigned.

Before the hysterectomy procedure, each patient received ranitidine 150 mg orally. The general anesthetics thiopental and propofol were used for all patients. Rocuronium or vecuronium was used for muscle relaxation. A preoperative antibiotic, either cefazolin (1 g) or cefotetan (1 g), was given intravenously. PCA was started in the Post-Anesthetic Care Unit. The PCA device was programmed to deliver 1-mL doses of medication—either ketamine and morphine combined or morphine alone—with a bolus dose of 2 mL permitted and a lock-out time of 6 min. The aim of the lock-out period is to prevent overdose through excessive demands for analgesia. Postoperative antiemetics were allowed at the discretion of the anesthesiologist, who used a standardized postoperative nausea and vomiting protocol specific to the hospital. If nausea and vomiting occurred, the patient was to receive dimenhydrinate initially, followed by metoclopramide. If nausea and vomiting continued, ondansetron was to be given.

The pharmacist collected data on postoperative days 1, 2, and 3 during ward rounds, using validated tools to assess pain, nausea and vomiting, sedation, dizziness, hallucination, nightmares, and dreams. The visual analogue scale is a sound methodologic instrument for quantitative assessment of postoperative pain at rest,[9-12] and is more sensitive than a verbal rating scale.[9-12] Therefore, a visual analogue scale was used in this study to assess the level of pain at rest (0 = no pain, 10 = worst pain).[13] The level of nausea and vomiting was assessed with a numeric 5-point verbal rating scale (0 = no nausea, 5 = extreme nausea, followed by vomiting). Level of sedation was assessed by the 5-point Observer's Assessment of Alertness/Sedation scale (where 1 = responds to name, 2 = lethargic, 3 = responds to name presented in a loud tone, 4 = responds after shaking, and 5 = does not respond).[14] Dysphoric experience, which includes dizziness, hallucinations, nightmares, and dreams, was also assessed with a 5-point scale (0 = none, 5 = extreme dizziness, hallucinations, nightmares, and dreams). Total consumption of the treatment drug was recorded on a pain assessment sheet, using data from the PCA device; the standard in-house preprinted physician's order for PCA was used for all patients.

The outcomes for the 2 treatment groups were compared with the Mann-Whitney *U* test,[15] which is appropriate for comparing 2 unpaired groups with ordinal data for the outcome measures. To ensure a conservative analysis, given the small sample size and use of convenience sampling, the Mann-Whitney *U* test was also used to examine differences between groups in terms of demographic data and total consumption of medication.

RESULTS

A total of 30 women enrolled and completed the study, 15 in each treatment group. There were no differences between the 2 groups with regard to age, height, weight, or body mass index (Table 1). None of the patients required PCA for more than 2 postoperative days. All of the patients were included in the analysis, and descriptive statistics were used to report the number of patients experiencing pain and other adverse effects on postoperative days 1 and 2 (Tables 2 and 3, respectively).

There were no significant differences between the treatment groups for the primary outcome measure of pain at rest, either 24 h after surgery ($p = 0.27$) or 48 h after surgery ($p = 0.96$). Similarly, there were no significant differences between the groups in terms of secondary outcomes (nausea and vomiting, sedation,

Table 1. Demographic Data for Patients Who Underwent Hysterectomy

Characteristic	Medication; Mean Value		*p* value
	Ketamine + Morphine (*n* = 15)	Morphine Alone (*n* = 15)	
Age (years)	49.2	47.4	0.95
Weight (kg)	71.6	76.7	0.16
Height (cm)	161.3	161.6	0.95
Body mass index (kg/m^2)	27.2	29.3	0.13

Table 2. Adverse Effects on Postoperative Day 1

Rating of Adverse Effect	No. of Patients		*p* value*
	Ketamine + Morphine (*n* = 15)	Morphine Only (*n* = 15)	
Pain			0.27
0 (none)	0	0	
1–3 (mild)	7	9	
4–7 (moderate)	7	6	
8–10 (severe)	1	0	
Nausea and vomiting			0.73
0 (none)	7	5	
1 (mild)	1	1	
2 or 3 (moderate)	5	5	
4 or 5 (severe)	2	4	
Sedation			0.09
0 (none)	6	1	
1 (mild)	0	1	
2 or 3 (moderate)	6	6	
4 or 5 (severe)	3	7	
Dizziness			0.33
0 (none)	5	5	
1 (mild)	0	1	
2 or 3 (moderate)	7	9	
4 or 5 (severe)	3	0	
Hallucination			>0.99
0 (none)	13	13	
1 (mild)	1	0	
2 or 3 (moderate)	0	2	
4 or 5 (severe)	1	0	
Nightmares			0.59
0 (none)	13	12	
1 (mild)	2	2	
2 or 3 (moderate)	0	1	
4 or 5 (severe)	0	0	
Dreams			0.79
0 (none)	11	11	
1 (mild)	2	0	
2 or 3 (moderate)	2	4	
4 or 5 (severe)	0	0	

*Mann–Whitney *U* test.

dizziness, hallucinations, dreams, and nightmares) measured on postoperative days 1 and 2.

The mean total consumption of morphine was 129 mg in the group receiving morphine only and 60 mg in the group receiving ketamine and morphine combined (the latter group also received 60 mg of ketamine). There was no significant difference between the 2 groups in the total amount of drug used over 48 hours ($p = 0.89$).

DISCUSSION

This prospective randomized study did not support the hypothesis that low-dose ketamine and morphine, administered in combination, would result in less pain than morphine alone. In addition, the combination therapy was not associated with less nausea and vomiting or fewer psychotomimetic effects than morphine alone, and there was no difference in the total amount of drug required.

In 2001, Burstal and others[16] concluded that the potential usefulness of ketamine after hysterectomy was offset by a high incidence of adverse effects and that the combination of ketamine and morphine could not be recommended for routine care. These researchers used a 2:1 ratio of ketamine to morphine, whereas the current study used a 1:1 ratio; this difference may account for

Table 3. Adverse Effects on Postoperative Day 2

Rating of Adverse Effect*	No. of Patients		*p* value†
	Ketamine + Morphine (*n* = 15)	Morphine Only (*n* = 15)	
Pain			0.96
0 (none)	9	7	
1–3 (mild)	2	7	
4–7 (moderate)	4	1	
8–10 (severe)	0	0	
Nausea and vomiting			0.70
0 (none)	11	10	
1 (mild)	2	2	
2 or 3 (moderate)	1	1	
4 or 5 (severe)	1	2	
Sedation			0.87
0 (none)	11	11	
1 (mild)	1	1	
2 or 3 (moderate)	2	3	
4 or 5 (severe)	1	0	
Dizziness			0.15
0 (none)	10	13	
1 (mild)	0	0	
2 or 3 (moderate)	5	2	
4 or 5 (severe)	0	0	

*No patients reported hallucinations, nightmares, or dreams on postoperative day 2.
†Mann–Whitney *U* test.

difference in frequency of adverse effects between the 2 studies (adverse effects were similar in the 2 groups in the current study). Sveticic and others[17] analyzed 12 combinations of ketamine and morphine and found that a 1:1 ratio, with a lock-out period of 8 min, yielded optimum results. Sveticic and others[17] reported lower pain scores and fewer side effects with the 1:1 ratio. We used a 1:1 ratio and a lock-out period of 6 min, almost identical with what is known as the "optimum combination", but were unable to reproduce the results of Sveticic and others.[17]

The current study was underpowered because of the small sample size. The differences in outcomes did not reach statistical significance, but a trend was noted descriptively. Specifically, postoperative pain after abdominal hysterectomy was consistently higher with low-dose ketamine and morphine administered together by PCA device than with morphine alone (see Tables 2 and 3).

We used abdominal hysterectomy for this study because this surgical procedure was performed often at our hospital, which made patient enrollment easier, and because the use of PCA for managing postoperative pain is common for this type of surgery. In addition, patients undergoing total abdominal hysterectomy have a high risk of postoperative nausea and vomiting.[18] In this study, there was no difference in pain between the 2 treatment groups; however, mean intensity of nausea and vomiting was higher for the morphine group on both postoperative days 1 and 2. Similarly, there was no difference in degree of dizziness, hallucinations, and dreams between the 2 groups on postoperative day 1 and very little difference on postoperative day 2. Interestingly, on postoperative day 1, fewer patients in the group receiving ketamine and morphine group experienced sedation.

The limitations of this study include the fact that it was not sufficiently powered to detect a small difference in outcomes. The small sample size means that the results obtained cannot be extended to the general population and must be interpreted with caution. In addition, it was not known whether the patients were opioid naïve or if they were receiving psychotropic medications, as these data were not collected. Data were collected on postoperative days 1 and 2, but these intervals might have been too long; it might have been more meaningful to collect data every 4 or 6 h. In addition, postoperative nausea and vomiting might have been influenced by the effect not only of the morphine but also of general anesthesia, the timing of administration of analgesia, the dose used, and the type of surgery. In this study, it was not possible to differentiate between

these potentially explanatory factors. More importantly, nausea and vomiting were treated with antiemetics, including dimenhydrinate, metoclopramide, and ondansetron during the data-collection period, which could have affected the outcomes, even though validated data collection tools were used.

CONCLUSIONS

In contrast to other studies,[4-6] we found that the addition of ketamine to morphine for PCA did not reduce pain scores or adverse effects for patients who had undergone abdominal hysterectomy.

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Appendix 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Inpatient at the study hospital	Admission for reason other than hysterectomy
Sex female	Previous experience of adverse effects of morphine administered by patient-controlled analgesia
Age = 21 years	
Hysterectomy indicated	
Patient preference for patient-controlled analgesia	Allergy to ketamine or morphine
No documented allergy to morphine or ketamine	