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# Preoperative Oral Morphine and Sub-Anesthetic Ketamine Co-Administration Reduce Acute Post-Mastectomy Pain

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## Abstract

**Objectives:** To assess the analgesic efficacy and tolerability of co-administration of pre-emptive single oral dose of sustained release morphine and sub- anesthetic ketamine infusion for modified radical mastectomy (MRM) with axillary evacuation.

**Methods:** Sixty four adult female patients scheduled for MRM were divided to two groups, morphine group (n=32) received preoperative oral sustained release morphine tablet, 30 mg and placebo group (n=32) received placebo tablet. Both groups received preoperative ketamine bolus, 0.5 mg/kg followed by continuous infusion 0.1 mg/kg/h for 24 h postoperatively. VAS pain score, time to first analgesic request, 24 h analgesic consumption were reported.

**Results:** The mean VAS pain score during movement was significantly decreased in morphine group in comparison to placebo group from 2 h till 72 h postoperatively, 2 h (2.87 ± 1.0 *vs.* 4.53 ± 1.67) mean difference (-1.67) (95% CI)-(2.38-0.95), 72 h (1.20 ± 0.76 *vs.* 1.83 ± 0.91) mean difference (-0.63) (95% CI)-(1.07-0.20) while the mean VAS pain score during rest was significantly decreased in morphine group in comparison to placebo group from 2 h till 24 h postoperatively, 2 h (2.03 ± 0.85 *vs.* 3.47 ± 0.93) mean difference (-1.33) (95% CI)-(1.78-0.90), 24 h (1.40 ± 0.72 *vs.* 1.77 ± 0.68) mean difference (-0.37) (95% CI)-(0.73-0.01).

The median (IQ) time to first analgesic request was significantly delayed in morphine group in comparison to placebo group, 11.8 (9.7:14.2) h *vs.* 2.3 (2.1:2.5) h, (P<0.001).

The number (percentage) of patients required paracetamol in the first postoperative 24 h was significantly lower in morphine group in comparison to placebo group, 10 (33%) *vs.* 30 (100 %) (P<0.001).

**Conclusion:** Analgesic technique based on pre-emptive sustained release oral morphine and perioperative infusion of sub-anesthetic dose of ketamine provides satisfactory analgesia for patients undergoing MRM.

**Keywords:** Oral morphine; Ketamine; Mastectomy

## Introduction

It is estimated that more than 50% of women will suffer moderate to severe acute pain following breast cancer surgery. It seriously affects quality of life through the combined impact of physical disability and emotional distress [1]. Surgical trauma induces hyperalgesia and allodynia. These enhanced reactions to noxious or non-noxious stimuli result from peripheral and/or central sensitization [2,3].

Pre-emptive analgesia is the administration of a drug before the onset of a painful stimulus that could reduce pain to a much greater extent than when the drug administered after the painful stimulus [4]. Opioids are considered the foundation of standard analgesic regimens for moderate-to-severe pain [5]. In addition to the broad value of morphine derivatives in clinical practice, their use as analgesic premedication before general anesthesia has aroused increasing interest [6]. Regularly dosed oral morphine has gained acceptance as the treatment of choice for patients with chronic cancer pain but is rarely used to treat acute postoperative pain. Ketamine has been used for treatment of acute pain. It is N-methyl-D-aspartate receptor (NMDA-R) antagonist [7], exerts anti-allodynic effect through induction of synthesis and release of nitric oxide [8]. It binds to mu-receptors to increase the effectiveness of opioid-induced signalling [9]. Previous studies have found that co-administration of parenteral ketamine and morphine decrease intensity of pain as well as side effects [10,11], however, some studies revealed no benefit [12,13]. The analgesic efficacy of pre-emptive oral morphine and parenteral ketamine infusion is not studied before, so the aim of this study is to assess the analgesic efficacy and tolerability of preoperative single oral dose of sustained release morphine in patients receiving continuous infusion of sub- anesthetic dose of ketamine for patients undergoing MRM.

## Methods

The study was approved by Institutional Ethics Committee of South Egypt Cancer Institute, the ethical approval number is (SECI20150196). Assuit University and a written informed consent for participation in the current clinical trial were obtained from each patient.

### Inclusion and exclusion criteria

Sixty four adult women, American Society of Anesthesiologists (ASA) physical status class I and II, scheduled for modified radical mastectomy with axillary evacuation were included. The exclusion criteria were patients with known allergy or intolerance to any of the drugs used in the trial, pregnancy, history of drug abuse, preoperative opioid medication, history of postoperative nausea and vomiting (PONV), and history of ileus, liver dysfunction and patients suffering from uncontrolled hypertension or ischemic heart disease.

### Randomization and blindness

Patients were randomly assigned to one of two groups: morphine group (n=32), where patients received orally 2 h before surgery sustained release morphine tablet (MST) 30 mg or placebo group (n=32), where patients received placebo tablet 2 h before surgery. The hospital pharmacists performed the randomization schedule using a computer-generated random number list. They masked the study medication by packing placebo and MST into two identical capsules in color and appearance to make the drugs unrecognizable. The study drugs were packed in opaque plastic containers labelled with the randomization numbers. The randomization code was opened at the end of the study.

### Interventions

The night before surgery (in the anesthesia clinic), each patient was instructed how to evaluate their own pain intensity using the Visual Analogue Scale (VAS), scored from 0 to 10 (where 0=no pain and 10 = the worst pain imaginable).

In the preoperative area (2 hours before the operation), patients received the concerned study drug; morphine (MST) 30 mg tablet or placebo tablet according to randomization schedule.

In the operative room, monitoring probes (ECG, pulse oximeter and none invasive blood pressure) were attached and a peripheral venous line was established.

Both groups were administered intravenous ketamine bolus, 0.5 mg/kg, just before induction of anesthesia, followed by 0.1 mg/kg/h continuous intravenous infusion for 24 h postoperatively. General anesthesia was induced with propofol 2-3 mg/kg and fentanyl 2 μg/kg, followed by cisatracurium 0.15 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane in 40% oxygen in air and cisatracurium 0.03 mg/kg on demand. Heart rate and mean arterial blood pressure (MAP) were maintained within 20% of the preoperative baseline values by giving IV bolus doses of fentanyl 50 μg if the MAP or heart rate increased more than 20% from the baseline values. Ephedrine 10 mg was given IV as needed to keep MAP more than 65 mm Hg. Atropine 0.01 mg/kg was given IV if heart rate decreased less than 50 beat/ minute.

Before skin closure, all patients received IV paracetamol, 1 gm. The postoperative analgesia consisted of intravenous paracetamol (1 gm) infusion on demand in the first postoperative day and if the patient is still in pain, rescue analgesia with intravenous morphine, 5 mg diluted in 5 ml saline was administered by a nurse. In the subsequent postoperative days (in the home), analgesia was provided through regular paracetamol tablets, 1 gm every 8 h. Moderate to severe PONV was treated with IV ondansetron 4 mg. No other analgesics or anti-emetics were administered during the first 24 postoperative hours.

### Assessments and outcomes

Time to first request for analgesic medication and the first 24 h analgesic consumption were recorded. Intensity of pain, assessed at rest and during movement, defined as (elevation of the arm from adduction to 90 degree abduction). Nausea and sedation were evaluated by the patients on a verbal rating scale scored from 0 to 3: none, light, moderate, and severe nausea or sedation. The need for anti-emetics in the first 24 hours postoperatively was recorded. Episodes of hallucinations, dizziness or nightmares were recorded by asking the patient 24 h postoperatively. Other potential side effects were recorded.

Primary outcome variable was the intensity of pain assessed with VAS pain score at rest and movement measured at the following postoperative time points (2, 6, 12, 24) h in the hospital by a nurse and at (36, 48, 72) h in home through a telephone. The secondary outcome variables were time to first analgesic request as well as 24 h analgesic consumption and morphine-ketamine related adverse events (nausea, vomiting, sedation, episodes of hallucinations and dizziness or night mares).

### Statistical analysis

Statistical analysis was carried out on a personal computer using SPSS version 22 software. The primary outcome (the VAS pain score) was normally distributed using the Anderson-Darling test and comparisons between groups were done by unpaired student's t test and subsequent analysis was achieved by linear mixed effect model for repeated measures examining the following effects: group, time, and group-by-time interaction. While the secondary outcome variable, time to first analgesic request was not normally distributed and expressed as medians (IQ range) and comparison between groups was done by the Mann-Whitney U test and elucidated by Kaplan-Meier survival analysis. Qualitative data were reported as counts and percentages, and differences between groups were analyzed with the $\chi^2$ test or Fisher exact test, as appropriate, where continuous data were described as mean ± standard division (SD) and (95% confidence interval), $P<0.05$ was considered statistically significant. Based on a preliminary pilot study of 10 patients in each group, we reported a mean ± SD of placebo group=4 ± 1.67 and a mean ± SD of morphine group=3.1 ± 1 Therefore, it was estimated that a minimum sample size of 29 patients in each study group would achieve a power of 80%, assuming a type I error of 0.05. We enrolled 64 patients to allow for dropouts.

## Results

Eighty patients were assessed for eligibility and sixty patients completed the study. The flow of patients through the study was illustrated in Figure 1.

Demographic data and patient's characteristics were similar between groups (Table 1).

The mean VAS pain score during movement was significantly decreased in morphine group in comparison to placebo group at all measured time points during the first 72 h postoperatively, while the mean VAS pain score during rest was significantly decreased in morphine group in comparison to placebo group during the first postoperative 24 h only. Detailed data was shown in (Table 2).

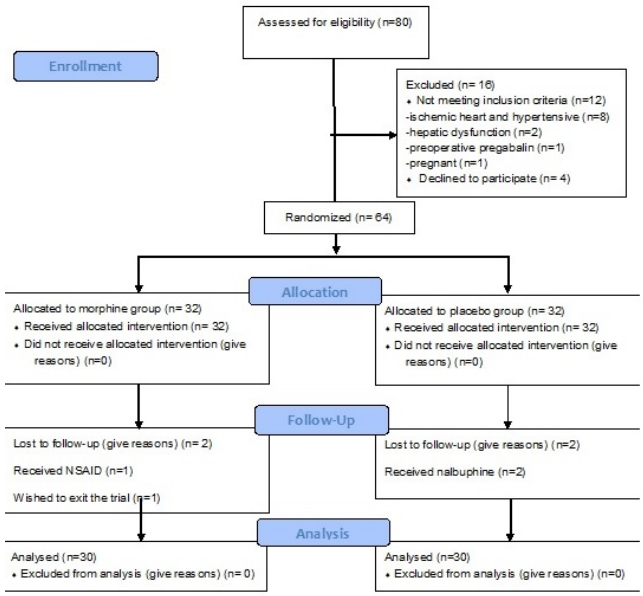


**Figure 1:** The flow of patients through the study.

| Variable | Morphine group (n=30) | Placebo group (n=30) | P value |
|---|---|---|---|
| Age (years) | 46.7 ± 7.8 | 43.4 ± 7.3 | 0.087 |
| Weight (Kg) | 79.2 ± 16.3 | 77.4 ± 12.4 | 0.120 |
| Height (Cm) | 166.9 ± 5.2 | 162.8 ± 5.4 | 0.961 |
| **ASA grade, n (%)** | | | |
| I | 18 (60.0%) | 20 (66.7%) | 0.789 |
| II | 12 (40.0%) | 10 (33.3%) | |
| Duration of surgery (min) | 140.9 ± 38.3 | 130.5 ± 27 | 0.693 |
| Duration of anesthesia (min) | 148.3 ± 38.3 | 142 ± 25.8 | 0.458 |

Data was presented as means ± SD or counts and percentages

**Table 1:** Demographic data and patient's characteristics.

| Variable | Morphine N=30 | Placebo N=30 | Mean difference | 95% CI (mean difference) |
|---|---|---|---|---|
| **VAS at movement** | Mean ± SD | Mean ± SD | | |
| 2 h | 2.87 ± 1.00* | 4.53 ± 1.67 | -1.67 | -(2.38-0.95) |
| 6 h | 2.67 ± 0.96* | 4.23 ± 1.14 | -1.57 | -(2.11-1.02) |
| 12 h | 2.47 ± 0.81* | 3.66 ± 0.88 | -1.57 | -(1.64-0.76) |
| 24 h | 2.10 ± 0.71* | 2.93 ± 0.58 | -0.83 | -(1.17-0.50) |
| 48 h | 1.53 ± 0.82* | 2.13 ± 0.57 | -0.60 | -(0.97-0.23) |
| 36 h | 1.70 ± 0.47* | 2.13 ± 0.51 | -0.43 | -(0.69-0.18) |
| 72 h | 1.20 ± 0.76* | 1.83 ± 0.91 | -0.63 | -(1.07-0.20) |
| **VAS at rest** | Mean ± SD | Mean ± SD | | |
| 2 h | 2.03 ± 0.85* | 3.47 ± 0.93 | -1.33 | -(1.78-0.90) |
| 6 h | 1.90 ± 0.92* | 3.33 ± 0.71 | -1.27 | -(1.68-0.85) |
| 12 h | 1.77 ± 0.97* | 2.37 ± 0.96 | -0.50 | -(0.98-0.02) |
| 24 h | 1.40 ± 0.72* | 1.77 ± 0.68 | -0.37 | -(0.73-0.01) |
| 48 h | 1.10 ± 0.48 | 1.23 ± 0.73 | -0.13 | -(0.45-0.19) |
| 36 h | 1.03 ± 0.56 | 1.20 ± 0.66 | -0.17 | -(0.48-0.15) |
| 72 h | 0.60 ± 0.68 | 0.77 ± 0.73 | -0.17 | -(0.53-0.20) |
| Footnote: *=p value<0.05 | | | | |

**Table 2:** postoperative VAS pain score at movement and rest.

The median (IQ) time to first analgesic request was significantly delayed in morphine group in comparison to placebo group, 11.8 (9.7:14.2) h *vs.* 2.3(2.1:2.5) h, (p<0.000) (Table 3).

| variable | Morphine (n=30) | Placebo (n=30) | P value |
|---|---|---|---|
| Time to first analgesic request (h) | 11.8(9.7:14.2) | 2.3 (2.1:2.5) | 0.00 |
| Patients required analgesic in 24 h (n, %) | 10 (33%) | 30 (100) | 0.00 |
| paracetamol (1 gm) (n, %) | 8 (26.7%) | 1 (3.33%) | 0.02 |
| paracetamol (2 gm) (n, %) | 2 (6.7%) | 12 (40%) | 0.01 |
| paracetamol (3 gm) (n, %) | 0 | 16 (53.3%) | 0.00 |
| Patients required morphine (5 mg) (n, %) | 0 | 8 (26.7%) | 0.00 |
| Patients required morphine (10 mg) (n, %) | 1 (3.33%) | 2 (6.7%) | 0.05 |
| Footnote: Data was presented as median (1Q) range and numbers (percentages). | | | |

**Table 3:** Duration of postoperative analgesia and analgesic consumption.

Regarding postoperative analgesic consumption, the number (percentage) of patients required postoperative paracetamol was significantly lower in morphine group in comparison to placebo group, 10 (33%) *vs.* 30 (100%) (p<0.001). The number (percentage) of patients required paracetamol in the first 24 h postoperatively was in morphine group *vs.* placebo group, paracetamol (1 gm) 8 (26.7%) *vs.* 1 (3.33%) (p<0.02), paracetamol (2 gm) 2 (6.7%) *vs.* 12 (40%) (p<0.01), paracetamol (3 gm) (0) *vs.* 16 (53.3%) (p<0.00) (Table 3). The number of patients required intravenous morphine was significantly lower in morphine group in comparison to placebo group 1 (3.33%) *vs.* 10 (33%) (Table 3).

The number of patients suffered from postoperative nausea and vomiting (PONV) was not statistically different between groups. The incidence of sedation was not statistically different between groups and none of the studied population suffered from excessive sedation. The number of patients complaining of dizziness was significantly increased in morphine group in comparison to placebo group (7 *vs.* 3) P<0.01). Detailed frequencies of adverse events were shown in Table 4.

| Variable | Morphine (n=30) | Placebo (n=30) |
|---|---|---|
| Sedation (none/mild/moderate/severe, n) | | |
| 2 h | 23/6/1/0 | 24/5/1/0 |
| 6 h | 22/8/0/0 | 27/3/0/0 |
| 12 h | 27/3/0/0 | 30/0/0/0 |
| 24 h | 30/0/0/0 | 29/1/0/0 |
| PONV (none/mild/moderate/severe, n) | | |
| 2 h | 22/6/1/1 | 25/4/1/0 |
| 6 h | 25/3/2/0 | 27/3/0/0 |
| 12 h | 27/3/0/0 | 29/1/0/0 |
| 24 h | 29/1/0/0 | 29/0/1/0 |
| Patients required ondansetron, (n) | 5 | 3 |
| Dose of ondansetron (4,8,16) mg | 4/1/0 | 2/1/0 |
| Patients hallucinating (n) | 1 | 2 |
| Patients with nightmares (n) | 2 | 1 |
| Patients with dizziness (n) | 7* | 3 |
| Footnote: *=p value<0.05 | | |

**Table 4:** Postoperative adverse events in the first postoperative 24 h.

## Discussion

The current study showed that preoperative medication with single dose oral morphine for patients receiving continuous infusion of sub-anesthetic dose of ketamine delayed time to first analgesic demand, reduced postoperative analgesic consumption and decreased the pain intensity during the first 72 h postoperatively without serious adverse events [14].

Opioids are still widely used prior to surgery to smooth induction of anesthesia, contribute to balanced anesthesia and provide postoperative pain relief. Morphine has been used as a premedication through different routes of administration including intra-muscular, oral sustained release and trans-buccal route [15-17].

The beneficial analgesic efficacy of combined ketamine and morphine administration was reported extensively in literature, In contrast to all previous studies that evaluated the addition of ketamine to PCA morphine for postoperative analgesia [10-12], the current study is unique in evaluation of analgesic efficacy of single oral dose of sustained release morphine for patients receiving continuous infusion of sub-anesthetic dose of ketamine. We found that two thirds of morphine group do not need any additional analgesics and expressed significantly lower VAS pain score for 72 h postoperatively.

The benefit of adding MST preoperatively is to supply the patients with a low and continuous dose of morphine in the initial postoperative phase, that should reduce overall analgesic consumption.

The rational of using continuous infusion of sub-anesthetic dosage of ketamine that started preoperatively and continued for 24 h postoperatively is firstly, acute post-mastectomy pain is essentially neuropathic due to surgical trauma of intercostal nerves, specifically intercosto-brachial nerves and ketamine is one of the effective drugs against neuropathic pain, secondly, it has been reported that perioperative ketamine may reduce the development of chronic postoperative pain *via* NMDA receptor blockade with subsequent reduction of wind-up and central sensitization [18].

The improvement in postoperative analgesia in the morphine group was consistent with previous study administered a single dose oral morphine, 10 or 20 mg for patients undergoing laparoscopic gastric bypass surgery [19].

Furthermore, it has been shown in two studies that oral and intramuscular pre-medication with morphine derivatives is able to reduce postoperative pain [20,21]. In contrast, other researchers observed no significant benefit of preoperative administration of sublingual buprenorphine or oral controlled-release morphine derivatives with regard to postoperative pain relief [22].

In the current study, we preferred to administer MST, 2 h before surgery as previous study reported that maximum plasma concentrations of morphine were recorded after 2.5 hours [23]. The smallest ketamine plasma concentration to counteract hyperalgesia while producing minimal side effects was shown to be 60 μg/ml [24]. This concentration was achieved by giving an initial bolus dose of ketamine 0.5 mg/kg, followed by a continuous infusion of 2 μg/kg/min [25], which was consistent with our study.

The improvement of analgesia produced by morphine-ketamine combination is explained by that painful stimulus activates NMDA receptors and produce hyperexcitability of dorsal root neurons. This induces central sensitization, expansion of the receptive field and wind-up phenomenon. Ketamine, a noncompetitive antagonist of NMDA receptors, can prevent the development of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon [26]. It has also been reported that mu-receptor activation by opioids leads to a sustained increase in glutamate synaptic effectiveness at the level of NMDA receptors. Moreover, opiates act at multiple sites in the central nervous system. Supraspinally, at locus ceruleus, nucleus raphe magnus, periaqueductal gray, medial thalamus, and limbic structures. Spinally, at the dorsal horn where the receptors are located pre- and postsynaptic [27,28]. Thus, MST when given preoperatively, it reduces pain impulses

arriving to the neuroaxis and subsequently prevention of central sensitization.

Study limitation deserves mentioning is we did not follow up patients for detection of chronic post-mastectomy pain as the study was powered only for detection of changes of acute pain intensity. Future studies should concentrate on the effect of morphine-ketamine co-administration on occurrence of chronic post-mastectomy pain. This combination may be of great value for operations with severe acute postoperative pain such as thoracotomy and spine surgeries.

In conclusion, analgesic technique based on pre-emptive sustained release oral morphine and perioperative infusion of sub-anesthetic dose of ketamine provides satisfactory analgesia for patients undergoing conservative breast cancer surgery.

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