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MORPHINE WITH ADJUVANT KETAMINE VS. HIGHER DOSES OF MORPHINE ALONE FOR IMMEDIATE POST-THORACOTOMY ANALGESIA

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Parts of this study were presented at the Euroanaesthesia 2003 Meeting, Glasgow, Scotland and at the 5th International Congress on Coronary Artery Disease, 2003, Florence, Italy.

No financial support was received for this clinical trial.
ABSTRACT

Background: Thoracotomy is associated with severe pain. We hypothesized that the concomitant use of a subanesthetic dose of ketamine plus a 75-standard morphine dose might provide more effective analgesia with fewer side effects than a standard morphine dose for early pain control.

Methods: We conducted a 6-month randomized, double blind study in patients undergoing thoracotomy for minimally invasive direct coronary artery bypass or for lung tumor resection. After extubation, when objectively awake (≥5/10 VAS) and complaining of pain (≥5/10 VAS), patients were connected to a PCIA delivering 1.5mg morphine/bolus (MO group) or 1.0mg morphine+5mg ketamine/bolus (MK group), with a 7-minute lockout time. Rescue intramuscular diclofenac 75mg was available. Follow-up lasted 4h.

Results: Forty-one patients completed the study. MO patients (n=20) used 6.8±1.9 (mean±SD) and 5.5±3.6 mg/h morphine during h 1 and 2, respectively; MK patients (n=21) used 3.7±1.2 and 2.8±2.3 mg/h, respectively (P<0.01). The 4-h activation rate of the device was double in the MOs than the MKs (66 ± 54 vs. 28 ± 20, P<0.001). The maximal self-rated pain score was 5.6±1.0 for the MO vs. 3.7±0.7 for the MK group (P<0.01). Four MO patients vs. one MK required diclofenac; 6 MO but no MK patients had SpO2 <94% on a FiO2=0.4 (P<0.01); two MO patients required re-intubation. PaCO2 was higher in the MO group (40±6 vs. 33±5 mmHg, P<0.05). Heart rate, blood pressure and incidence of nausea/vomiting were similar; no ketamine-related hallucinations were detected.

Conclusions: Subanesthetic ketamine combined with a 35%-lower morphine dose provided equivalent pain control compared to the standard morphine dose alone, with fewer adverse side effects and a 45%-reduction in morphine consumption.

Registered at this site ClinicalTrials.gov; Registration number NCT00625911
**KEY WORDS**: thoracotomy, analgesia, minimally invasive direct coronary artery bypass (MIDCAB), lung tumor, pain, postoperative, morphine, ketamine
### Abbreviation List

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CICU</td>
<td>cardiac intensive care unit</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>forced expiratory volume (in one second)/forced vital capacity</td>
</tr>
<tr>
<td>FiO₂</td>
<td>fraction of inspired oxygen</td>
</tr>
<tr>
<td>IQR</td>
<td>inter-quarterly ratio</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>MIDCAB</td>
<td>minimally invasive direct coronary artery bypass</td>
</tr>
<tr>
<td>MK group</td>
<td>morphine 1.0 mg + 5 mg ketamine /bolus</td>
</tr>
<tr>
<td>MO group</td>
<td>morphine 1.5 mg/bolus</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>arterial blood partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PACU</td>
<td>post-anesthesia care unit</td>
</tr>
<tr>
<td>PCIA</td>
<td>patient-controlled intravenous analgesia</td>
</tr>
<tr>
<td>PONV</td>
<td>postoperative nausea and/or vomiting</td>
</tr>
<tr>
<td>SpO₂</td>
<td>pulse-derived arterial blood oxygen saturation</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
</tbody>
</table>
INTRODUCTION

Thoracotomy, whether performed for the resection of lung tumor or for minimally invasive
direct coronary artery bypass, MIDCAB, surgery, is associated with severe and sometimes
uncontrolled, debilitating pain.1,2 Catecholamine release in response to nociceptive stimuli3 is
associated with undesirable hemodynamic consequences as well as disturbances in
respiratory, endocrine, metabolic4 and immune function.5 These changes may increase the
rate of complications, prolong hospitalization and augment cost.4-6 Importantly, if the acute
pain is not effectively controlled, it may evolve into severe chronic pain.7

Postoperative pain that is uncontrollable despite the administration of considerable
amounts of IV morphine could suggest tolerance to the drug.8-10 The administration of large
amounts of morphine to the awakening patient may cause respiratory and hemodynamic
depression.11,12 These effects may be especially serious when they follow lung lobectomy8 or
when they occur in patients with poor left ventricular function.13,14 For these reasons,
supplementation of morphine with non-narcotics (adjuvant agents) may be a way of
effectively controlling pain while reducing the incidence of adverse events.15,16

Ketamine, a noncompetitive NMDA-receptor antagonist, was shown to enhance
opioid-induced antinociception,17 to reduce hyperalgesia and to prevent morphine-induced
resistance18,19 and, when combined with morphine, to lower post operative morphine
consumption.20 Given that subanesthetic (≤500 mcg/kg) doses of ketamine seldom produce
undesired hemodynamic alterations (e.g., elevated heart rate and blood pressure),21 we
hypothesized that by combining a subanesthetic dose of ketamine with morphine, we could
effectively control pain, while reducing postoperative morphine demand and drowsiness, with
an acceptable level of adverse side effects. The primary end point was pain VAS that was
used to calculate the sample size (see statistical paragraph); the secondary parameters
measured were morphine consumption, PCA activation, and side effects.
PATIENTS AND METHODS

After the Ethics Committee of the Tel-Aviv Sourasky Medical Center approved this study’s protocol, 44 patients scheduled for elective MIDCAB or for lung resection via thoracotomy during a 6-month period (September 2001- March 2002) were enrolled in the study. They all gave their informed, written consent to participate in this double blind study and were randomly assigned to one of two groups according to their national ID number. Patients were eligible for the study if they had been referred for a first time isolated coronary bypass and if their surgeon considered them candidates for a MIDCAB procedure, or if they were to undergo lung surgery. Exclusion criteria were ASA physical class ≥3, emergency operations, Q-wave myocardial infarct occurring during the previous 3 weeks, or poor left ventricular function (e.g., EF <30% by echocardiography or angiography). Other exclusion criteria were: a BMI >35 kg/m², past or current neuropathy or psychological disturbances, the use of psychiatric medications, including anti-depressants and anti-psychotic agents, chronic liver or renal failure requiring dialysis, a FEV₁/FVC <70%, allergy to ketamine, morphine or NSAIDs, clotting abnormalities, a platelets count <70000/mm³, a white blood count <300<14000/mm³, uncontrolled diabetes mellitus or fasting blood glucose >250 g/dl, evidence of sepsis or infection up to one week prior to randomization. There was no age restriction.

Anesthesia protocol

General anesthesia was administrated by the same anesthetist and no regional block was used. Induction of the standardized anesthesia consisted of IV midazolam 2 mg, propofol 1 mg/kg, medium-dose fentanyl (5-15 mcg/kg) and pancuronium (0.1mg/kg) to facilitate endotracheal intubation. Anesthesia was maintained by repeated doses of fentanyl and pancuronium when deemed necessary. All patients were ventilated in a volume-controlled mode with a tidal
volume of 6 ml/kg and received oxygen enriched with isoflurane (0.4-0.8% inspired concentration). Neuromuscular relaxation was reversed pharmacologically at the end of surgery. When the patients resumed spontaneous respiration, responded adequately to orders and demonstrated negative inspiratory force of at least 20 cmH2O or vital capacity greater than 20 cc/kg, their tracheas were extubated. Patients who were not extubated in the operating room were excluded from the study (see “allocation” boxes in CONSORT Statement, Fig. 1).

The postoperative monitoring included the measurements of heart rate by a 5-lead electrocardiograph, invasive systolic and diastolic blood pressures, respiratory rate, and SpO2 (AS/3™, Datex-Ohmeda®, Helsinki, Finland).

Postoperative analgesia protocol

All patients were transferred to the PACU where postoperative follow-up started. They received IV analgesics (per patient request) starting from when their pain was score was \( \geq 5/10 \) on a 0-10 VAS, see below) and when the attending physician determined that the patient was in an acceptable cognitive state \( (\geq 5/10 \text{ VAS}) \). A cutoff pain score was chosen on the basis of previous experience in acute pain control. Drug injections consisted of either 1.5 mg morphine plus saline (group MO) or 1 mg morphine plus 5 mg ketamine (group MK). A blinded anesthesiologist prepared the separate syringes based on the randomization list and administered the first dose, after which the PCIA device was turned on. The device was preset to deliver similar boluses whenever the patient activated it, controlled by a 7-minute lockout period. If the protocol was ineffective to reduce pain VAS by \( \geq 2 \) levels or patients reported no satisfaction of the treatment within 30 minutes of treatment, a rescue dose of intramuscular diclofenac 75 mg was available by the nurses.

One of two designated PACU nurses, who were blinded to the drug assignment, assessed the variables listed below for each patient during the entire stay in the PACU. VAS scores were assessed every 15 minutes:
Subjective pain intensity was patient self-rated, based on a VAS graded from “no pain”=0 to “worst possible pain”=10.

A patient’s subjective level of wakefulness was assessed by a self-rated VAS, from 1=heavily sedated to 10=fully awake. If patients were asleep, they were awakened to obtain their rating; the data of patients unable to cooperate were excluded at that time point.

An SpO2-derived value of 94%, with 40% oxygen by facemask, was the lowest limit allowed for arterial oxygenation, otherwise a 100% oxygen mask was placed and the various patient’s data from that time point were not recorded.

Untoward effects (e.g., nausea, vomiting or any distress) were recorded by the nurse and treated as indicated (e.g., metoclopramide 10 mg IV for nausea or vomiting). Nurses specifically asked patients if hallucinations occurred and reported them.

Reintubation in the postoperative period, if necessary, was decided by the blinded PACU attending physician based on clinical and laboratory data.

Patients were kept for 4 h in the PACU and then were transferred to the CICU for further observation; no further data were collected thereafter.

Statistical analysis

The analyses were performed at the Statistical Laboratory of the School of Mathematics, Tel-Aviv University, using the SPSS Release for Windows, Version 11.01 (Chicago, IL, 2002). A pre-study power table where delta (representing the mean difference in pain score recorded in a pilot study)=2.1, alpha=0.05 and power=0.97 resulted in the need for a minimum of 15 patients in each group. The demographic data (age, weight) and background characteristics (baseline heart and respiratory rates, SpO2, systolic and diastolic blood pressures), the ASA physical class, duration of surgery and intraoperative drug dosages, as well as fluid and blood administration, were compared using one-way analysis of variance (ANOVA). Patients’
gender and intra-group procedure distributions were analyzed using the Fisher exact test. The rates of the hourly demands of the PCIA devices were square rooted in order to obtain their normal distribution; the results were then analyzed by one-way ANOVA with repeated measures. The number of times the patients received a rescue drug and the rate of side effects were also analyzed using the Fisher exact test. The effects of type of analgesia on the patients’ self-rated pain and grade of wakefulness (VAS's), as well as the hourly amounts of analgesic use were also analyzed using the ANOVA with repeated measures. The ANOVA tests were always followed by the post-hoc Tukey’s Honest Significant Difference method. All values are expressed as mean ± standard deviation (SD), with significance defined as \( P \leq 0.05 \).

**RESULTS**

Out of 62 screened patients, 44 fulfilled the study criteria for randomization. Three of them subsequently dropped out after surgery because they required continuous ventilation (CONSORT statement, Fig. 1); no MIDCAB patient was converted to an on-pump procedure. The demographic, anesthesia and surgical data were similar between the two drug study groups (Table 1); intraoperative blood replacement and fluid infusion were similar as well (data not shown). Baseline (immediately before starting study drug administration) vital signs, patients’ self-rated pain intensity (Fig. 2) and wakefulness scores (data not shown) were also similar between the groups.

Overall, the amounts of analgesics that were requested by the patients to alleviate pain were found to be associated with the drug regimen. The MK group required 45% of the total amount of morphine used by the MO group (\( P < 0.001 \)), ranges being 16-19 mg/4h, and applied the PCIA more frequently (66 ± 54 vs. 28 ± 20, \( P < 0.001 \), Fig. 3). The MO group
requested more diclofenac per the protocol (P=NS) than the MK group (Table 1); in all cases the rescue treatment was effective.

The subjectively evaluated pain intensity (VAS) during the 4-h PACU stay was significantly (P<0.001) lower for the MK group compared to their MO counterparts (Fig. 2), despite the larger amount of morphine that had been administered to the latter group. The subjectively rated wakefulness scores for the MK group were also better (p<0.05) than those for the MO group (Table 1).

All the recorded respiratory parameters were better in the MK group compared to the MO group (Table 1): none of the MK patients had an SpO₂ <94% with 40% oxygen by facemask, but 6 of the MO patients did at one time point each (P<0.01): SpO₂ values improved better in the former than in the latter (Table 1) and PaCO₂ were also lower in the former. Two of the latter group subsequently required re-intubation and mechanical ventilation for a period of 5-6 hours due to clinical respiratory distress associated with an increase in heart rate and systolic blood pressure. The mean 4-h-respiratory rate was also better in the MK group than in the MO group (Table 1). Finally, 1 h after the drugs were first injected, heart rate and blood pressures in both groups decreased and stabilized for the rest of the study period: interestingly, they were almost identical in both study groups (Fig. 4).

The incidence of PONV was similar between the groups (Table 1); all incidents were short-lived and responded well to appropriate therapy. One MK patient reported a sensation of lightheadedness that resolved spontaneously in <4 minutes, and at no time did any patients report hallucinations or postoperative confusion.

None of the study patients in either group were kept in the PACU for more than the protocol dictated period and all were transferred to the ward after fulfilling PACU discharge criteria. All the study patients were later discharged from the CICU uneventfully according to the cardiothoracic departmental discharge policies.
DISCUSSION

Our study demonstrates that the administration of an IV subanesthetic dose (5 mg/bolus) of ketamine combined with 1/5 of the standard (1.5 mg) morphine dose provided lower subjective measures of pain (by >2 points on a scale of 1-10) than the standard morphine dose alone during the immediate (4 h) post-thoracotomy period. The combined protocol was also associated with remarkably stable hemodynamic conditions and better respiratory parameters than the MO group. These objective effects were associated with a better self-rated level of wakefulness, similar PONV, and insignificant ketamine specific side effects.

Postoperative pain ranks among the major problems of surgical patients, especially after thoracotomy.22 During the last few years, evaluation of intense pain associated with thoracotomy has become a subject of considerable interest, since both lung resection and MIDCAB share the properties of newly evolving minimally invasive and “fast-tracking” surgical techniques.23

Ketamine hydrochloride is a well known general dissociative anesthetic and a short acting analgesic with antagonist activity at the NMDA receptor. Morphine and other opioids produce antinociception via mu receptor agonistic activity and by the activation of the monoaminergic descending pathways at the spinal level,10 they also activate the NMDA receptor, resulting in hyperalgesia and development of tolerance to opioids.3,10 If tolerance is one of the explanations for severe postoperative pain small doses of ketamine added to morphine could treat pain better than morphine alone.8,10

If given alone, ketamine in small doses (<250 mcg/kg IV) may seldom induce a change in level of consciousness lasting a few minutes because of the large plasma concentration that develops immediately after the injection.24 Whereas the plasma half-life of ketamine is only 15-20 minutes, the analgesic effect of the MK combination was evident and
clinically stable throughout the 4-h observation period. The drug combination dose that was used in this study allowed for a prompt reduction of pain and a morphine sparing effect. These current results are supported by our previous data\textsuperscript{25} that demonstrated the beneficial combination of ketamine and morphine in patients suffering from severe postoperative pain that was resistant to morphine.

Heart rate and blood pressure are negatively affected by large morphine doses given within a short period of time, but most importantly, respiratory rate, oxygenation and adequate ventilation may drastically worsen because of the increased sedation.\textsuperscript{4,12} We observed such events in several individuals in the MO group. On the other hand, the ketamine dose of anesthesia is known to increase heart rate and blood pressure due to its pro-adrenergic effect: our MK patients did not exhibit these reactions, either because of the very low ketamine dose and/or because of its combination with morphine. The evidence of almost identical pulse rates and blood pressures in both groups is, therefore, promising, especially in the MIDCAB subgroup of patients of this study.

Reducing postoperative pain enhances the ability to breathe deeply and cough effectively. All these features lead to better oxygenation and a probable preservation of positive myocardial oxygen balance.

Ketamine alone may produce drowsiness;\textsuperscript{21,26} our MK patients, however, self-rated themselves more awake than their MO counterparts, supporting the findings of an earlier report.\textsuperscript{25} Short lived hallucinations are the most frequently mentioned side effect of ketamine, especially if administered at doses $\geq500$ mcg/kg.\textsuperscript{27,28} Some reports indicated that up to 30\% of the patients receiving IV anesthesia doses of ketamine (0.5-1.5 mg/kg) experienced unpleasant dreams or acute psychosis-like symptoms.\textsuperscript{29} In our current MK study group, there were no reports of hallucinations or bad dreams, a finding we consider to be due to the small intermittent dosage.\textsuperscript{25}
This study is limited by the short duration of follow up. The results of this study cannot be extrapolated to imply that improving pain for the initial 4 postoperative h has long-term effects on pain control or overall recovery. Nevertheless, effective initial pain control is an important factor among other determinants of safe recovery and patient satisfaction. Also, the specific cohort of coronary bypass patients presented here was managed with the "fast track" mode of immediate awakening and extubation, the success of this approach is dependent, among other things, on level of pain, wakefulness and adequate pulmonary function. Indeed, the ketamine+morphine group fared significantly better in all of these parameters. Another limitation is the theoretical difference between the incisions used for the MIDCAB vs. the lung lobectomy. MIDCAB’s were performed via an anterolateral incision, with the patients lying in the supine position, whereas lung resections were performed via a more lateral incision, with the patients positioned more laterally. However, both types of incision were similarly represented in both study groups. One other potential limitation to the analysis of our data is the possibility of inter-observer variability between the PACU nurses who collected the data. To minimize variability, there were only 2 dedicated nurses in the PACU who assumed responsibility for the study patients.

In conclusion, immediate (4 h) postoperative subanesthetic doses of ketamine added to ½ the standard dose of morphine provided equivalent analgesia with a better safety profile compared to that obtained by a standard dose of morphine alone, in patients undergoing thoracotomy for lung tumor resection or MIDCAB. The MK patients were hemodynamically stable and there were signs of less respiratory depression compared to the MO group. MK patients self-rated their wakefulness as being better than the MO patients. We recommend additional studies to confirm our findings so that this promising drug protocol can be considered safe for use in postoperative pain control of pulmonary and cardiac patients.
Acknowledgment: The authors thank Esther Eshkol, MA (institutional medical copyeditor, Tel Aviv Sourasky Medical Center) for editorial assistance, and the nursing staff of the PACU for their collaboration and dedication.
REFERENCES


Table 1. Demographic, intraoperative and 4h-postoperative data (mean ± SD or absolute numbers).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Morphine (n=20)</th>
<th>Morphine+Ketamine (n=21)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>58 ± 12</td>
<td>61 ± 11</td>
<td>0.41</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>73 ± 8</td>
<td>76 ± 14</td>
<td>0.4</td>
</tr>
<tr>
<td>Male/Female*</td>
<td>13/9</td>
<td>10/12</td>
<td>0.16</td>
</tr>
<tr>
<td>MIDCAB/lung surgery (n)*</td>
<td>7/15</td>
<td>6/16</td>
<td>0.25</td>
</tr>
<tr>
<td>Duration of surgery (h)*</td>
<td>3.1 ± 1.3</td>
<td>3.5 ± 1.0</td>
<td>0.28</td>
</tr>
<tr>
<td>MO 1&lt;sup&gt;st&lt;/sup&gt;-h consumption (mg)</td>
<td>6.8 ± 1.9</td>
<td>3.7 ± 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>MO 2&lt;sup&gt;nd&lt;/sup&gt;-h consumption (mg)</td>
<td>5.5 ± 3.6</td>
<td>2.8 ± 2.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Diclofenac consumption (n)</td>
<td>4</td>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>Maximal pain (VAS 0-10)**</td>
<td>5.6 ± 1.0</td>
<td>3.7 ± 0.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>90-min arterial blood pCO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>40 ± 6</td>
<td>33 ± 5</td>
<td>0.0003</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt; changes over 90min (%)***</td>
<td>1.0±1.0</td>
<td>4.5±1.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Respiratory rate (breaths/minute)</td>
<td>19 ± 1</td>
<td>13 ± 1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Wakefulness score (VAS 1-10)</td>
<td>3.2 ± 1.2</td>
<td>5.5 ± 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Incidence of PONV (n)</td>
<td>3</td>
<td>1</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Including data of the excluded (2 MO and 1 MK) patients; statistical analyses followed the intent-to-analyze format. **Collected before patient's discharge. ***Difference between baseline and 90-min values.
Figure legends.

Fig. 1. CONSORT statement of the study.

Fig. 2. Four-hour pain trends (mean ± SD).

VAS, visual analogue scale.

*P<0.001 (by ANOVA with repeated measures).

Fig. 3. Square-rooted number of PCIA device applications (median and IQR).

*P<0.0001 (by ANOVA with repeated measures).

Fig. 4. Four-hour hemodynamics (systolic and diastolic blood pressures and heart rate) (mean ± SD).
Fig. 1. Flow diagram of the progress through the phases of the randomized trial.
Fig. 2.

![Graph showing Pain VAS (0-10) over Time (min) of observation for Morphine (MO) and Morphine+Ketamine (MK).]
Fig. 3.
Fig. 4.

![Graph showing blood pressures or heart rate over time.](image-url)

- SBP-MO
- SBP-MK
- DBP-MO
- DBP-MK
- HR-MO
- HR-MK

Blood pressures (mmHg) or heart rate (bpm) vs. Time (min) of observation.
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