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Morphine With Adjuvant Ketamine vs Higher Dose of Morphine Alone for Immediate Postthoracotomy Analgesia

Nachum Nesher, MD; Margaret P. Ekstein, MD; Yoseph Paz, MD; Nissim Marouani, MD; Shoshana Chazan, RN; and Avi A. Weinbroum, MD

Background: Thoracotomy is associated with severe pain. We hypothesized that the concomitant use of a subanesthetic dose of ketamine plus a two-third-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 visual analogue scale [VAS]) and complaining of pain (> 5/10 VAS), patients were connected to patient-controlled IV analgesia delivering 1.5 mg of morphine plus saline solution (MO) or 1.0 mg of morphine plus a 5-mg ketamine bolus (MK), with a 7-min lockout time. Rescue IM diclofenac, 75 mg, was available. Follow-up lasted 4 h.

Results: Forty-one patients completed the study. MO patients (n = 20) used 6.8 ± 1.9 mg/h (mean ± SD) and 5.5 ± 3.6 mg/h of morphine during the first and second hours, respectively; MK patients (n = 21) used 3.7 ± 1.2 mg/h and 2.8 ± 2.3 mg/h, respectively (p < 0.01). The 4-h activation rate of the device was double in the MO patients than in the MK patients (66 ± 54 vs 28 ± 20, p < 0.001). The maximal self-rated pain score was 5.6 ± 1.0 for the MO group vs 3.7 ± 0.7 for the MK group (p < 0.01). Four MO patients vs one MK patient required diclofenac; 6 MO patients but no MK patients had oxygen saturation by pulse oximetry < 94% on a fraction of inspired oxygen of 0.4 (p < 0.01); two MO patients required reintubation. Paco2 was higher in the MO group (40 ± 6 mm Hg vs 33 ± 5 mm Hg, p < 0.05). Heart rate, BP, 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.

Trial registration: ClinicalTrials.gov Identifier: NCT00625911

(CHEST 2009; 136:245–252)

Abbreviations: ANOVA = analysis of variance; CONSORT = Consolidated Standards of Reporting Trials; MIDCAB = minimally invasive direct coronary artery bypass; MK = 1.0 mg of morphine plus 5-mg ketamine bolus; MO = 1.5 mg of morphine plus saline solution; NMDA = N-methyl-D-aspartate; PACU = postanesthesia care unit; PCIA = patient-controlled IV analgesia; PONV = postoperative nausea and/or vomiting; SpO2 = pulse-derived arterial blood oxygen saturation; VAS = visual analogue scale

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 Catecholaminel release in response to nociceptive stimuli3 is associated with undesirable hemodynamic consequences as well as disturbances in respiratory, endocrine, metabolic,4 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.\textsuperscript{8–10} The administration of large amounts of morphine to the awakening patient may cause respiratory and hemodynamic depression.\textsuperscript{11,12} These effects may be especially serious when they follow lung lobectomy,\textsuperscript{2} or when they occur in patients with poor left ventricular function.\textsuperscript{13,14} For these reasons, supplementation of morphine with nonnarcotics (adjuvant agents) may be of a way of effectively controlling pain while reducing the incidence of adverse events.\textsuperscript{15,16} Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist, was shown to enhance opioid-induced antinociception,\textsuperscript{17} to reduce hyperalgesia and to prevent morphine-induced resistance\textsuperscript{18,19} and, when combined with morphine, to lower postoperative morphine consumption.\textsuperscript{20} Given that subanesthetic (\(\leq 500 \mu g/kg\)) doses of ketamine seldom produce undesired hemodynamic alterations (eg, elevated heart rate and BP),\textsuperscript{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 visual analogue scale (VAS) that was used to calculate the sample size (see “Statistical Analysis” section); the secondary parameters measured were morphine consumption, patient-controlled IV analgesia (PCIA) device activation, and side effects.

**Materials and Methods**

This study is one part of a larger study conducted in the Post Anesthesia Care Unit on patients from the Department of Cardiovascular and Thoracic Surgery at the Tel-Aviv Sourasky Medical Center during the period 2001–2004 and had been approved by the Ethics Committee of the institution. The present

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Parts of this study were presented at the Europeananaesthesia 2003 Meeting, Glasgow, Scotland May 31–June 3, 2003; and at the fifth International Congress on Coronary Artery Disease, Florence, Italy, October 19–22, 2003.

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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 to 15 \(\mu g/kg\); and pancuronium, 0.1 \(mg/kg\), to facilitate endotracheal intubation. Anesthesia was maintained by repeated doses of fentanyl and pancuronium when deemed necessary. All patients received ventilated in volume-controlled mode with a tidal volume of 6 mL/kg and received oxygen enriched with isoflurane (0.4 to 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 cm H\(_2\)O or vital capacity \(>20 \text{ mL/kg}\), their tracheas were extubated. Patients who were not extubated in the operating room were excluded from the study (see “allocation” boxes in Consolidated Standards of Reporting Trials [CONSORT] statement; Fig 1).

The postoperative monitoring included the measurements of heart rate by a 5-lead ECG, invasive systolic BP and diastolic BP, respiratory rate, and pulse-derived arterial blood oxygen saturation (\(\text{SpO}_2\)) [AS/3; Datex-Ommeda; Helsinki, Finland].

Postoperative Analgesia Protocol

All patients were transferred to the postanesthesia care unit (PACU), where postoperative follow-up started. They received IV analgesics (per patient request) starting from when their pain score was \(\geq 5/10\) on a 0- to 10-point VAS) 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.\textsuperscript{2,12} Drug injections consisted of either 1.5 \(mg\) of morphine plus saline solution (MO) or 1 \(mg\) of morphine plus 5-\(mg\) ketamine bolus (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
Figure 1. Flow diagram of the process through the phases of the randomized trial; from CONSORT statement.
Statistical Analysis

Statistical analysis was performed at the Statistical Laboratory of the School of Mathematics, Tel-Aviv University (SPSS Release for Windows, version 11.01; SPSS; Chicago, IL). A presudy 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 BP, diastolic BP), the American Society of Anesthesiologists 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). Gender and intragroup procedure distributions were analyzed using the Fisher exact test. The rates of the hourly demands of the PCA devices were square-rooted in order to obtain their normal distributions; 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), 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 key honest significant difference method. All values are expressed as mean $\pm$ SD, with significance defined at $p \leq 0.05$.

Results

Of 62 screened patients, 44 patients fulfilled the study criteria for randomization. Three patients subsequently dropped out after surgery because they required continuous ventilation (CONSORT statement, Fig 1); no MIDCAB patient was converted to an on-pump procedure. 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, 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 ($p < 0.001$) [range, 16 to 19 mg/4 h], and applied the PCA less frequently (28 $\pm$ 20 times vs 66 $\pm$ 54 times, $p < 0.001$; Fig 3). The MO group requested more diclofenac per the protocol ($p = 0.0001$) 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 the 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 six of the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Morphine Plus (n = 20)</th>
<th>Ketamine (n = 21)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr*</td>
<td>58 $\pm$ 12</td>
<td>61 $\pm$ 11</td>
<td>0.41</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>73 $\pm$ 8</td>
<td>76 $\pm$ 14</td>
<td>0.4</td>
</tr>
<tr>
<td>Male/female gender*</td>
<td>13/9</td>
<td>10/12</td>
<td>0.16</td>
</tr>
<tr>
<td>MIDCAB/lung surgery*</td>
<td>7/15</td>
<td>6/16</td>
<td>0.25</td>
</tr>
<tr>
<td>Duration of surgery, h*</td>
<td>3.1 $\pm$ 1.3</td>
<td>3.5 $\pm$ 1.0</td>
<td>0.28</td>
</tr>
<tr>
<td>MO first-hour consumption, mg</td>
<td>6.8 $\pm$ 1.9</td>
<td>3.7 $\pm$ 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>MO second-hour consumption, mg</td>
<td>5.5 $\pm$ 3.6</td>
<td>2.8 $\pm$ 2.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Diclofenac consumption</td>
<td>4</td>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>Maximal pain (VAS 0–10)†</td>
<td>5.6 $\pm$ 1.0</td>
<td>3.7 $\pm$ 0.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>90-min Paco2, mm Hg</td>
<td>40 $\pm$ 6</td>
<td>33 $\pm$ 5</td>
<td>0.0003</td>
</tr>
<tr>
<td>SpO2 changes over 90 min, %‡</td>
<td>1.0 $\pm$ 1.0</td>
<td>4.5 $\pm$ 1.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>19 $\pm$ 1</td>
<td>13 $\pm$ 1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Wakefulness score, VAS 1–10</td>
<td>3.2 $\pm$ 1.2</td>
<td>5.5 $\pm$ 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Incidence of PONV</td>
<td>3</td>
<td>1</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are presented as mean $\pm$ SD or No.
*Including data of the excluded patients (MO, n = 2; MK, n = 1); statistical analysis followed the intent-to-analyze format.
†Difference between baseline and 90-min values.
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 reintubation and mechanical ventilation for a period of 5 to 6 h due to clinical respiratory distress associated with an increase in heart rate and systolic BP. 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 BPs in both groups decreased and stabilized for the rest of the study period: interestingly, they were almost identical in both study groups (Fig 4).

Figure 2. Four-hour pain trends (mean ± SD). *p < 0.001, ANOVA with repeated measures.

Figure 3. Square-rooted number of patient-controlled IV analgesia device applications (median and interquartile range). *p < 0.0001, ANOVA with repeated measures.
The incidence of postoperative nausea and/or vomiting (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 $\frac{1}{10}$ min, 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 cardiac ICU 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 two thirds of the standard (1.5-mg) morphine dose provided lower subjective measures of pain (by $\geq 2$ points on a scale of 1 to 10) than the standard morphine dose alone during the immediate (4 h) postthoracotomy 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.\textsuperscript{2,23} During the last few years, evaluation of intense pain associated with thoracotomy has become a subject of considerable interest because both lung resection and MIDCAB share the properties of newly evolving minimally invasive and “fast-tracking” surgical techniques.\textsuperscript{24}

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\textsuperscript{10}; they also activate the NMDA receptor, resulting in hyperalgesia and development of tolerance to opioids.\textsuperscript{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.\textsuperscript{8,10}

If administered alone, ketamine in small doses ($<250 \mu g/kg$ 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.\textsuperscript{25} Whereas the plasma half-life of ketamine is only 15 to 20 min, the

![Figure 4. Four-hour hemodynamics (systolic BP [SBP], diastolic BP [DBP], and heart rate [HR]; [mean ± SD]).](image-url)
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\(^{26}\) that demonstrated the beneficial combination of ketamine and morphine in patients with severe postoperative pain that was resistant to morphine.

Heart rate and BP are negatively affected by large morphine doses administered within a short period of time, but most importantly, respiratory rate, oxygenation, and adequate ventilation may drastically worsen because of the increased sedation.\(^{4,12}\) We observed such events in several individuals in the MO group. However, the ketamine dose of anesthesia is known to increase heart rate and BP due to its proadrenergic 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 BPs in both groups is, therefore, promising, especially in the MIDCAB subgroup of patients.

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\(^{21,27}\); our MK patients, however, self-rated themselves more awake than their MO counterparts, supporting the findings of an earlier report.\(^{26}\) Short-lived hallucinations are the most frequently mentioned side effect of ketamine, especially if administered at doses \(\geq 500 \mu g/kg\).\(^{28,29}\) Some reports\(^{30}\) indicated that up to 30% of the patients receiving IV anesthesia doses of ketamine (0.5 to 1.5 mg/kg) had unpleasant dreams or acute psychosis-like symptoms. 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.\(^{26}\)

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-plus-morphine group fared significantly better in all of these parameters. Because of this limitation and in order to ascertain if this 4-h effect is sustained, we followed a subsequent group of cardiothoracic patients for a period of 72 h; the results indeed demonstrated a sustained effect over the first 3 postoperative days.\(^{22}\)

Another limitation is the theoretical difference between the incisions used for the MIDCAB vs the lung lobectomy. MIDCAB surgeries 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 are the possibility of interobserver variability between the PACU nurses who collected the data. To minimize variability, there were only two dedicated nurses in the PACU who assumed responsibility for the study patients.

In conclusion, immediate (4 h) postoperative subanesthetic doses of ketamine added to two thirds 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. 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 did 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 for pulmonary and cardiac patients.

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