Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain?

Timothy J. Mathews*a, Antonia M.D. Churchhousea, Tessa Housdena and Joel Dunningb

a Department of Thoracic Surgery, Royal Infirmary of Edinburgh, Edinburgh, UK
b Department of Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, UK

* Corresponding author. 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA, UK. Tel: +44-757-2417545; e-mail: timjmathews@gmail.com (T.J. Mathews).

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Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was 'is the addition of ketamine to morphine patient-controlled analgesia (PCA) following thoracic surgery superior to morphine alone'. Altogether 201 papers were found using the reported search, of which nine represented the best evidence to answer the clinical question. This consisted of one systematic review of PCA morphine with ketamine (PCA-MK) trials, one meta-analysis of PCA-MK trials, four randomized controlled trials of PCA-MK, one meta-analysis of trials using a variety of peri-operative ketamine regimes and two cohort studies of PCA-MK. Main outcomes measured included pain score rated on visual analogue scale, morphine consumption and incidence of psychotomimetic side effects/hallucination. Two papers reported the measurements of respiratory function. This evidence shows that adding ketamine to morphine PCA is safe, with a reported incidence of hallucination requiring intervention of 2.9%, and a meta-analysis finding an incidence of all central nervous system side effects of 18% compared with 15% with morphine alone, \( P = 0.31, \) RR 1.27 with 95% CI (0.8–2.01). All randomized controlled trials of its use following thoracic surgery found no hallucination or psychological side effect. All five studies in thoracic surgery (\( n = 243 \)) found reduced morphine requirements with PCA-MK. Pain scores were significantly lower in PCA-MK patients in thoracic surgery papers, with one paper additionally reporting increased patient satisfaction. However, no significant improvement was found in a meta-analysis of five papers studying PCA-MK in a variety of surgical settings. Both papers reporting respiratory outcomes found improved oxygen saturations and PaCO2 levels in PCA-MK patients following thoracic surgery. We conclude that adding low-dose ketamine to morphine PCA is safe and post-thoracotomy may provide better pain control than PCA with morphine alone (PCA-MO), with reduced morphine consumption and possible improvement in respiratory function. These studies thus support the routine use of PCA-MK instead of PCA-MO to improve post-thoracotomy pain control.

Keywords: Review • Ketamine • Morphine • Analgesia • Patient-controlled

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients undergoing thoracic surgery] is a patient-controlled analgesia (PCA) [consisting of ketamine with morphine] or [morphine alone] the best for [post-operative analgesia].

CLINICAL SCENARIO

You have just started a video-assisted thoracoscopic surgery lobectomy programme and have been impressed by their lack of pain. Unfortunately, your thoracotomy patients are still in pain despite paravertebrals, PCAs, nefopam, paracetamol and non-steroidal anti-inflammatory drugs. You talk to an anaesthetist who has just come from the pain service, who suggests adding ketamine to the morphine PCA. You are anxious about episodes of psychosis so you resolve to check the literature for this new method of analgesia.

SEARCH STRATEGY

Medline was searched from 1948 to June week 5 2011 using the OVIDSP interface.

(ketamine.mp. OR exp Ketamine/)AND(morphine.mp. OR exp Morphine/OR exp Morphine Derivatives/)AND(exp Post-operative Complications/OR post-operative.mp. OR patient controlled analgesia.mp. OR exp Analgesia, Patient-Controlled/OR PCA.mp).

Studies were included if they compared morphine PCA (PCA-MO) with morphine and Ketamine PCA (PCA-MK) in any...
specialty. We also added any studies on ketamine in thoracotomy wounds.

**SEARCH OUTCOME**

Two hundred and one papers were found using the reported search. From these, nine papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

**RESULTS**

**Safety**

Subramaniam et al. [2] performed a meta-analysis of six trials \( n = 330 \) comparing PCA-MK with PCA-MO. 18% of PCA-MK patients reported central nervous system (CNS) side effects compared with 15% of PCA-MO patients, \( P = 0.31 \), seven trials \( n = 289 \) using IV-ketamine infusion were identified, with 149 patients receiving ketamine. No significant increase in CNS side effects was noted in this group (15 of 149, vs 9 of 140, \( P = 0.09 \)).

Sveticic et al. [3] reported an incidence of hallucination/vivid dreams requiring the intervention of 2.9%, and incidence requiring no intervention of 3.3% in a prospective cohort study of 1026 patients receiving PCA-MK post-operatively in a variety of surgical settings.

In Carstensen and Moller’s [4] qualitative systematic review of 11 randomized controlled trials (RCTs) looking at PCA-MK in a range of different surgical settings \( n = 887 \) of whom 448 received ketamine, nine studies \( n = 746 \) found no significant increase in psychotomimetic side effects with PCA-MK and two \( n = 141 \) did.

All four RCTs of PCA-MK in thoracic surgery [5–8] reported no hallucinations or psychological side effect in the MK group.

**Morphine consumption**

Carstensen and Moller’s [4] qualitative review found six studies \( n = 305 \) showing significantly reduced morphine consumption in the PCA-MK group compared with the PCA-MO group, and five studies \( n = 582 \) did not.

Bell et al. [9] performed meta-analysis on 24 h IV-PCA morphine consumption from 10 trials \( n = 432 \) using a variety of methods of ketamine administration peri-operatively. They found that treatment with ketamine reduced morphine consumption.

Chazan et al. [5] reported the reduced cumulative morphine usage in the PCA-MK group following various transthoracic procedures.

Nesher et al. [6] reported reduced morphine consumption over hours 1 and 2 post-thoracotomy in PCA-MK patients \( P = 0.0001 \) and \( P = 0.008 \) respectively. This was repeated in their further study [7] which found reduced morphine consumption over 24 h in PCA-MK patients following thoracotomy \( P < 0.05 \).

Michelet et al. [8] found no significant difference in morphine consumption with PCA-MK in the first 24 h post-thoracotomy. Reduced morphine consumption was found, however, at 36 h \( P = 0.029 \), 48 h \( P = 0.007 \) and 60 h \( P = 0.006 \).

Atanagana et al. [10] found reduced total morphine consumption with PCA-MK following thoracic surgery \( MO = 52, SD 12; MK = 31.5, SD 16, P < 0.05 \).

**Pain control**

Carstensen and Moller’s [4] qualitative systematic review of RCTs reported six studies \( n = 333 \) showed significantly lower pain scores with PCA-MK compared with MO. Four studies \( n = 512 \) showed no significant difference. All three thoracic surgery studies \( n = 148 \) showed significantly lower pain scores with PCA-MK. Subramaniam et al. [2] performed meta-analysis on six trials \( n = 330 \) comparing PCA-MK and PCA-MO in a variety of surgical settings. They found a weighted mean difference (WMD) of −5.4 mm visual analogue scale (VAS) with ketamine (95% CI, −1.25, 0.18), this difference was not significant.

Chazan et al. [5] found lower pain scores following various transthoracic procedures in the PCA-MK group over days 1–3, but this difference was not significant until day 3 \( P = 0.0001 \). They found significantly increased patient satisfaction in the MK group over days 1–3 \( P = 0.012 \). Similarly, Michelet et al. [8] found no significant difference in pain scores between PCA-MK and PCA-MO patients until 48 h and 60 h post-thoracotomy \( P < 0.05 \).

Nesher et al. [6] found reduced maximal pain scores over 4 h post-thoracotomy in PCA-MK patients compared with MO \( MO = 5.6, SD 1.0; MK = 3.7, SD 0.7; P = 0.0001 \). This was followed up by a further RCT by Nesher et al. [7], which found consistently significantly reduced pain scores in the PCA-MK group following thoracotomy \( P = 0.03 \). They also reported a reduced requirement for IV-PCA at 36 h in the MK group \( P = 0.008 \).

Atanagana et al.’s [10] cohort study of thoracic patients found reduced pain scores on coughing at 12 h and 24 h post-operatively with PCA-MK compared with PCA-MO \( P < 0.05 \).

**Respiratory function**

Nesher et al. [6] reported reduced PaCO₂ at 90 min post-thoracotomy with PCA-MK compared with PCA-MO \( MO = 40 mmHg, SD 6; MK = 33 mmHg, SD 5; P = 0.0003 \) and a greater percentage increase in SpO₂ over 90 min post-operatively \( MO = 1.0, SD 1.0; MK = 4.5, SD 1.0; P = 0.0001 \). The respiratory rate was higher at 4 h post-operatively in MO compared with MK patients \( P = 0.0001 \). In their follow-up study, Nesher et al. [7] found no PCA-MK patients desaturated below SpO₂ of 94% with 40% oxygen facemask following thoracotomy, whereas seven MO patients did \( P < 0.001 \).

Michelet et al. [8] found the reduced incidence of nocturnal desaturation over the first three nights post-thoracotomy with PCA-MK compared with PCA-MO \( P < 0.001, P = 0.021 \) and \( P = 0.0019 \). They also found a greater decrease in FEV₁ in the MO group on post-operative day 1 \( P = 0.039 \), this difference was lost by day 2.

**CLINICAL BOTTOM LINE**

Adding ketamine to morphine PCA is safe, with reported incidence of hallucination requiring intervention of 2.9% [3], and a meta-analysis [2] finding an incidence of all CNS side effects of 18% compared with 15% with morphine alone. All trials of its use following thoracic surgery found no hallucination or psychological side effect. All five thoracic surgery studies \( n = 243 \) found reduced morphine requirements with PCA-MK, with a
<table>
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<tr>
<th>Author, date and country, study type (level of evidence)</th>
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<tr>
<td><strong>Subramaniam et al., 2004, USA [2]</strong></td>
<td>37 RCTs (total of 2385 patients) of ketamine added to opioid analgesia for post-operative pain relief following various surgical procedures, using a variety of ketamine regimes were included. Studies were divided into five subgroups: IV ketamine as single dose (n = 11), continuous infusion (n = 6), epidural ketamine with opioid (n = 8) and studies in children (n = 4)</td>
<td>Mean resting pain scores (VAS) for the first 24 h was analysed with available data from five PCA studies</td>
<td>Overall WMD of −5.4 mm (95% CI: −1.25, 0.18). No significant difference</td>
<td>A discrepancy was noted between the total number of patients in IV PCA-MK trials and the data given in analysis of CNS side effects without clear explanation in the paper</td>
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<td><strong>Sveticic G et al., 2005, Switzerland [3]</strong></td>
<td>1026 patients undergoing various elective surgical procedures under general anaesthetic received post-operative PCA consisting of morphine and ketamine in the 1:1 ratio, initially given as 1.5 mg of bolus of each drug and increased as needed in 0.5 mg increments to the maximum of 2.5 mg</td>
<td>Incidence of vivid dreams or hallucinations (%)</td>
<td>Present but no intervention needed (not unpleasant) = 3.3 Reduction in PCA bolus needed = 0.8 Pharmacological intervention needed = 0 Termination of PCA therapy needed = 2.1 Total = 6.2</td>
<td>In all cases of vivid dreams/hallucinations requiring discontinuation of the therapy, symptoms fully resolved in 1-2 h</td>
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<td><strong>Carstensen and Moller, 2010, Denmark [4]</strong></td>
<td>Eleven studies were identified that included 887 patients undergoing various surgical procedures, in which the intervention was post-operative IV PCA consisting of boluses of ketamine with opioid compared with post-operative IV PCA with opioid alone</td>
<td>Pain score measured by patient self-reporting using VAS or verbal rating scale</td>
<td>Six studies (n = 333, average quality score = 4.8) showed a statistically significant decrease in pain intensity with ketamine compared with morphine alone. Four studies found no improvement in pain when adding ketamine to morphine (n = 512, average quality score = 4.3). All three studies with patients undergoing thoracic surgery found a significantly improved pain score with the addition of ketamine (n = 148, average quality score = 5)</td>
<td>No meta-analysis was performed due to heterogeneity of the data. Various dosing strategies were used. Some numerical errors were apparent in the paper</td>
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<tr>
<td><strong>T.J. Mathews et al. / Interactive CardioVascular and Thoracic Surgery</strong></td>
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<td>Chazan et al., 2010, Israel [5]</td>
<td>46 patients undergoing various thoracic surgical procedures (minimally invasive direct coronary artery bypass, off-pump coronary artery bypass or thoracotomy) were randomized to receive post-operative IV PCA with either 2 mg of morphine bolus alone (group MO) or 1 mg/5 mg of morphine + ketamine bolus, respectively (MK)</td>
<td>Cumulative morphine usage (mg)</td>
<td>MO = 78, SD 48; MK = 48, SD 34, P = 0.01&lt;br&gt;MO = 2.4, SD 1.8; MK = 1.8, SD 1.1, P = 0.01 (given as P = 0.0001 in graph)</td>
<td>No change in mood or cognitive state observed in ketamine patients&lt;br&gt;Patients pain POD3 data P = 0.1 in table, but shown as P = 0.0001 in graph</td>
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<td>Nesher et al., 2009, Israel [6]</td>
<td>41 patients undergoing unspecified thoracotomy for elective MIDCAB or lung resection were randomized to receive post-operative IV PCA of boluses of either 1 mg of morphine plus saline (group MO) or 1 mg of morphine + 5 mg of ketamine (MK)</td>
<td>Morphine consumption (mg)</td>
<td>First hour: MO = 6.8, SD 1.9; MK = 3.7, SD 1.2; P = 0.0001&lt;br&gt;Second hour: MO = 5.5, SD 3.6; MK = 2.8, SD 2.3; P = 0.008</td>
<td>One MK patient reported episode of light-headedness that resolved spontaneously in &lt;4 min. No MK patients reported hallucinations or post-operative confusion. Incidence of post-operative nausea and vomiting similar between two groups</td>
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<td>Nesher et al., 2008, Israel [7]</td>
<td>58 patients undergoing anterolateral thoracotomy for MIDCAB, lung tumour resection or median sternotomy for OPCAB were randomized to receive post-operative IV PCA boluses of 1.5 mg of morphine alone (group MO) or 1 mg of morphine + 5 mg of ketamine (group MK), both with lockout time of 7 min</td>
<td>Morphine consumption (mg/patient/h) over 24 h (VAS)</td>
<td>MO = 2.0, SD 2.3; MK = 1.0, SD 1.4; P = 0.05&lt;br&gt;Consistently and significantly lower in the MK group than the MO group (P = 0.03)</td>
<td>No ketamine-specific side effects observed</td>
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<td>Michelet et al., 2007, France [8]</td>
<td>48 patients undergoing lobectomy were randomized to receive post-operative PCA consisting of either morphine 1 mg/ml (group MO) or morphine with ketamine 1 mg/ml of each (MK), bolus dose of 0.015 ml/kg with 10 min lockout time</td>
<td>Cumulative morphine consumption (mg)</td>
<td>No significant difference at 0–24 h&lt;br&gt;At 36 h: MO = 43, SD 18; MK = 32, SD 14; P = 0.029&lt;br&gt;At 48 h: MK &lt; MO, P = 0.007&lt;br&gt;At 60 h: MK &lt; MO, P = 0.006</td>
<td>No psychological alteration or side effect related to ketamine use was noted</td>
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<td>Bell et al., 2005, Norway, Denmark, UK, Finland [9]</td>
<td>This was a qualitative and quantitative systematic review of RCTs of peri-operative administration of ketamine. Thirty-seven trials with a total of 2137 patients were included, with various methodologies of administration of ketamine peri-operatively for various surgical procedures. Post-operative PCA ketamine was used in four studies (n = 212, average quality score 3.5). Due to the heterogeneity of the trials, quantitative analysis was only performed on data on 24 h cumulative IV PCA morphine consumption (10 trials, n = 432) and post-operative nausea and vomiting (26 trials, n = 1261)</td>
<td>Cumulative PCA morphine consumption in first 24 h after surgery.</td>
<td>Treatment with ketamine reduced morphine consumption, WMD −15.98 mg with 95% CI (−19.70, −12.26)</td>
<td>The results of this meta-analysis should be interpreted with caution, as the timing and methodology of ketamine administration varied between trials used</td>
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<td>Atangana et al., 2007, Republic of Cameroon [10]</td>
<td>50 patients undergoing thoracic surgery [unspecified thoracotomy for intrathoracic tumours (n = 21), pleural decortications (n = 22) and thoracic trauma associated with multiple rib fractures or sternal fractures needing osteosynthesis (n = 7)] were allocated to receive post-operative PCA consisting of either 0.5 mg/ml of morphine with placebo (MO) or 0.5 mg/ml of morphine with 0.5 mg/ml of ketamine(MK), in boluses of 2 ml, with lockout time of 5 min</td>
<td>Pain on coughing (VAS)</td>
<td>At 12 h, MO = 5, MK = 3, P &lt; 0.05 At 24 h MO = 4, MK = 1, P &lt; 0.05</td>
<td>This study was non-randomized and non-blinded. No standard deviation was given in results for pain scores 'Dysleptic' effects absent in both groups</td>
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FEV₁
Greater decrease in FEV₁ in the MO group compared with the MK group on post-operative day 1 (P = 0.039)
No significant difference between FEV₁ in the MO group and the MK group on post-operative day 2.

Pain score (VAS)
0 h: MO = 50, SD 26; MK 50, SD 27; no significant difference
12 h: MO = 45, SD 20; MK = 38, SD 20; no significant difference
24 h: MO = 40, SD 20; MK = 30, SD 14; no significant difference
36 h: MO = 38, SD 22; MK 28, SD 12; no significant difference
48 h: MO = 42, SD 21; MK 29, SD 16; P < 0.05
60 h: MO = 36, SD 20; MK = 24, SD 13; P < 0.05

Second night: MO = 2.15 (0.35–8.65); MK = 0.5 (0.01–1.30); P = 0.021
Third night: MO = 2.46 (0.57–5.51); MK = 0.55 (0.21–1.00); P = 0.0019
trend towards decreased morphine consumption in other trials. Pain scores were significantly lower in PCA-MK patients in all thoracic surgery papers, with one paper additionally reporting increased patient satisfaction. Two papers reported respiratory outcomes and found improved oxygen saturations and PaCO₂ levels in PCA-MK patients following thoracic surgery. These studies thus support the routine use of PCA-MK instead of PCA-MO to improve post-thoracotomy pain control.

Conflict of interest: none declared.

REFERENCES