Systematic Review and Meta-Analysis

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Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses

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Abstract

Ketamine is often added to opioids in patient-controlled analgesia devices. We tested whether in surgical patients, ketamine added to an opioid patient–controlled analgesia decreased pain intensity by ≥25%, cumulative opioid consumption by ≥30%, the risk of postoperative nausea and vomiting by ≥30%, the risk of respiratory adverse effects by ≥50%, and increased the risk of hallucination not more than 2-fold. In addition, we searched for evidence of dose-responsiveness. Nineteen randomized trials (1349 adults, 104 children) testing different ketamine regimens added to various opioids were identified through searches in databases and bibliographies (to 04.2016). In 9 trials (595 patients), pain intensity at rest at 24 hours was decreased by 32% with ketamine (weighted mean difference −1.1 cm on the 0-10 cm visual analog scale [98% CI, −1.8 to −0.39], $P < 0.001$). In 7 trials (495 patients), cumulative 24 hours morphine consumption was decreased by 28% with ketamine (weighted mean difference −12.9 mg [−22.4 to −3.35], $P = 0.002$). In 7 trials (435 patients), the incidence of postoperative nausea and vomiting was decreased by 44% with ketamine (risk ratio 0.56 [0.40 to 0.78], $P < 0.001$). There was no evidence of a difference in the incidence of respiratory adverse events (9 trials, 871 patients; risk ratio 0.31 [0.06 to 1.51], $P = 0.08$) or hallucination (7 trials, 690 patients; odds ratio 1.16 [0.47 to 2.79], $P = 0.70$). Trial sequential analyses confirmed the significant benefit of ketamine on pain intensity, cumulative morphine consumption, and postoperative nausea and vomiting and its inability to double the risk of hallucination. The available data did not allow us to make a conclusion on respiratory adverse events or to establish dose-responsiveness.

Keywords: Patient-controlled analgesia, PCA morphine, Ketamine, Randomized controlled trial

1. Introduction

Intravenous patient-controlled analgesia (IV PCA) with opioids is widely used for postoperative pain management. This technique was shown to provide effective analgesia,[4,14,22] and to be associated with high patient satisfaction,[12,31] and improved safety compared with conventional opioid treatment.[52] However, the use of opioid IV PCA is often limited by opioid-related adverse effects such as postoperative nausea and vomiting (PONV) or respiratory depression. Also, concerns regarding opioid-induced hyperalgesia have grown, and opioid-sparing pain management strategies have been advocated.[19]

The rationale behind adding ketamine to an opioid for pain treatment is mainly supported by animal data.[28,30] Through its anti–N-methyl-D-aspartate properties, ketamine decreases wind-up, central sensitization, opioid tolerance, and opioid-induced hyperalgesia.[1,45,49]

Five systematic reviews of randomized controlled trials (RCT) have reached contradictory conclusions concerning the benefit of adding ketamine to intraoperative or postoperative opioids.[6,9,16,46,53] None controlled in their analyses for the risk of a type I error because of multiple outcomes and repeated significance testing, and the only one that was designed to specifically address the role of ketamine added to opioid PCA included trials that were published up to 2009.[9] Several relevant trials have been published since 2009.

This systematic review and meta-analysis was designed to update previously published evidence,[9] and to verify whether, in surgical patients, adding ketamine to an opioid in an IV PCA device decreased postoperative pain intensity, cumulative morphine consumption, and the risks of PONV or respiratory depression, without increasing the risk of hallucination. We adapted our analyses to take into account the risk of type I error because of repeated significance testing. We also aimed to check for evidence of dose-responsiveness.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Methods

2.1. Protocol and registration

The protocol for this systematic review is detailed in the Appendix (Appendix: Table A, available online at http://links.lww.com/PAIN/A339). We followed the PRISMA guidelines for reporting of meta-analyses of RCTs.

2.2. Eligibility criteria

We searched for RCTs comparing any opioid in an IV PCA for postoperative pain control (control group), with ketamine (any regimen) added to the same opioid in a PCA (experimental group). We included studies that were performed in adults or children undergoing any surgical procedures under general or regional anesthesia. We considered trials that reported postoperative cumulative opioid consumption, pain intensity, or incidence of opioid- or ketamine-related adverse effects. We did not consider studies if patients were undergoing surgery under sedation only or were receiving ketamine before or during the procedure through another route than through the PCA device, if a continuous infusion of ketamine was administered, or if additional analgesics were used in 1 treatment group only (ie the trial design was not strictly controlled). Animal studies, abstracts, or unpublished reports were excluded.

2.3. Information sources

We searched for articles in Medline (through PubMed), Cochrane Library, and Embase. The last searches were performed in April 2016. Bibliographies of selected articles were examined for additional references. We applied no language restriction.

2.4. Search

The key words used for our search were "patient-controlled analgesia," "PCA morphine," "ketamine," and "Randomized Controlled Trial," combined with Boolean "OR" and "AND."

2.5. Study selection

Retrieved articles were reviewed for inclusion based on title and abstract by one author (B.A.). Selected articles were then assessed regarding inclusion criteria by another author (N.E.). When no consensus could be reached, issues were resolved through discussion with a third author (M.R.T).

2.6. Data collection process

Data were extracted by 1 author (B.A.) and entered into an excel sheet that was specifically designed for the purpose of this study. The accuracy of extracted data was checked by another author (L.K.). Authors of original articles were contacted for missing data or when continuous summary measures were not reported as means with SD. If authors did not answer our inquiries and the data were reported in graphs only, we extracted the data from the graphs.

2.7. Data items

For each included article, we extracted information on study population, and ketamine and opioid regimens.

Primary endpoints were pain intensity (on a 0-to-10 cm visual analog scale [VAS]) and cumulative morphine consumption (mg) at 24 hours, and incidence of PONV, respiratory adverse events (including respiratory depression and episodes of desaturation), and hallucination.

Secondary endpoints included pain intensity and morphine consumption at other time points, and further drug-related adverse effects that were possibly related to the opioid or to ketamine. Pain intensity data from 0 to 10 point numerical scales or 0 to 100 mm VAS were converted to a 0 to 10 cm VAS. When it was unclear whether pain intensity was evaluated at rest or on movement, and the authors did not answer to our inquiry, we assumed it was pain at rest.

2.8. Risk of biases

We assessed the risk of biases in individual trials using the Cochrane tool,[21] which contains 6 items rated as low, high, or unclear risk of bias. Because small trials tend to overestimate treatment effects, we added "study size" as an additional criterion. For the purpose of this analysis, we arbitrarily defined a study size <50 patients (number of patients per group, <25) as high risk of bias (**Fig. 1**). One author (B.A.) scored all articles. This was independently checked by 2 coauthors (N.E., L.K.). Discrepancies were discussed with the fourth author (M.R.T.).

2.9. Summary measures and synthesis of results

2.9.1. Primary endpoints

Our assumption was that the minimal effect worth using ketamine as an adjuvant in an opioid IV PCA for postoperative pain control was a decrease in the cumulative 24 hours morphine consumption of ≥25% (from 50 mg to <35 mg), a decrease in pain intensity at 24 hours of ≥30% (from 4 to 3 cm on a 0-10 cm VAS), a decrease in the incidence of PONV of ≥30% (from 35% to 25%), and a decrease in the incidence of respiratory adverse events by more than 2-fold (from 10% to 5%). In addition, to be considered safe, we expected that ketamine would not increase the incidence of hallucination by more than 2-fold (from 5% to 10%).

2.9.2. Secondary endpoints

Pain intensity and cumulative morphine consumption after 24 hours, and further drug-related adverse events were extracted as reported in the original trials.

2.9.3. Analyses

Meta-analyses were performed when data from more than 3 trials or 100 patients could be combined.

For dichotomous outcomes, we computed risk ratios (RR), or Peto odds ratios for rare events, comparing experimental with

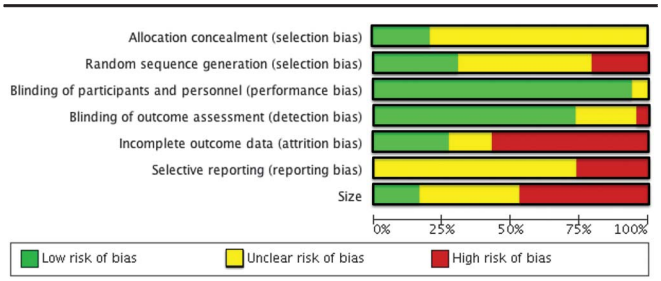

Figure 1. Risk of bias graph. Review authors' judgments about each risk of bias item presented as percentages across all included studies. For the size item, low risk = >100 patients per study, unclear risk = 50–100 patients per study, and high risk = <50 patients per study.

control groups at study level, based on the number of events reported in each group and group sizes. We combined the effect estimates of individual studies into a pooled weighted estimate using Mantel–Haenszel or Peto weights. In case of zero events, a constant continuity correction was applied by adding 0.5 to each cell.

For continuous outcomes, we computed the mean differences in effects between experimental and control groups at study level. Mean differences were combined into a pooled weighted mean difference (WMD). A fixed effect model was used to combine homogenous data. When the reported data were heterogeneous ($P < 0.1$ or $I^2 > 50\%$), we performed subgroup analyses to search for reasons underlying this heterogeneity. If a source of heterogeneity was identified, subgroup analyses were reported. If none was found, we used a DerSimonien and Laird random effects model to pool the data.

To minimize the chance of type I errors when analyzing 5 primary endpoints, we modified the usual threshold for statistical significance to an alpha-level of 0.02 (5% divided by half of the number of primary endpoints). Accordingly, 98% confidence intervals (CI), rather than the conventional 95% CI, were computed around the point estimates. For secondary endpoints, 95% CI were computed.

For all primary outcomes, we performed trial sequential analyses to identify the "information size" required to verify our hypotheses. The information size is the number of patients needed to reach a definite conclusion of either efficacy or futility. If the information size was not reached, O'Brien-Fleming alpha-spending boundaries were computed. To reach a definite conclusion of effect, the cumulative Z-curve was expected to cross the upper boundary of the O'Brien-Fleming alpha-spending estimate.[48]

We checked for graphical evidence of dose-responsiveness by plotting on the forests plots the trials according to increasing ketamine regimens. In the absence of a graphical display suggesting dose-responsiveness, no further analyses were performed.

Analyses were performed using RevMan (Computer Program, version 5.3) and the Trial Sequential Analysis software (Copenhagen Trial Unit).[48]

3. Results

3.1. Study selection

We identified 220 articles; 26 potentially responded to our inclusion criteria (**Fig. 2**). Six articles were subsequently excluded since ketamine was used intraoperatively.[3,20,24,38,41,42] A further article, published in Chinese, could not be retrieved neither from the authors nor from the journal.[55] Finally, 19 RCTs with data from 1349 adults and 104 children were included.[2,8,10,11,13,23,25,29,32,34–36,39,40,43,47,50,51,56]

Our database overlapped with previously published similar systematic reviews.[6,9,16,46,53] Compared with Subramaniam et al[46] from 2004, we included 14 additional RCTs but excluded 2. Compared with Elia et al[16] from 2005, we included 13 additional trials. Compared with Bell et al[6] from 2006, we included 18 additional trials, but excluded 10. Compared with Carstensen et al[9] from 2010, we included 9 additional trials, but excluded 2. Finally, compared with the analysis by Wang et al[53] from 2016, we included 8 additional trials, but excluded 24 (including 5 published in Chinese that were not retrievable).

3.2. Study characteristics

The trials were published from 1996 to 2014 (**Table 1**). They originated from 12 countries: Israel (4 trials), Korea (3), Turkey, Iran, and Australia (2 each), and Canada, Egypt, France, Switzerland, Tunisia, and USA (1 each). Surgeries were abdominal and gynecological (7 trials), cardio-thoracic (6), and orthopaedic (6). The risks of biases are detailed in the Appendix (Appendix: Table B, available online at http://links.lww.com/PAIN/A339). Trial sizes ranged from 30 to 352 patients. The median of study size was 57; 9 studies included less than 50 patients. Four studies were performed by the same group of authors.[11,29,39,40]

Patient-controlled analgesia settings and drug regimens varied across studies. Three studies used a background infusion,[10,36,56] 13 used a lockout time,[8,10,11,13,23,29,32,34,36,39,40,47,56] and in 2, individual PCA settings were not standardized but determined by the anesthesiologist in charge of the patient.[43,51] Morphine was used in 15 trials, fentanyl in 2,[10,56] and tramadol[51] and

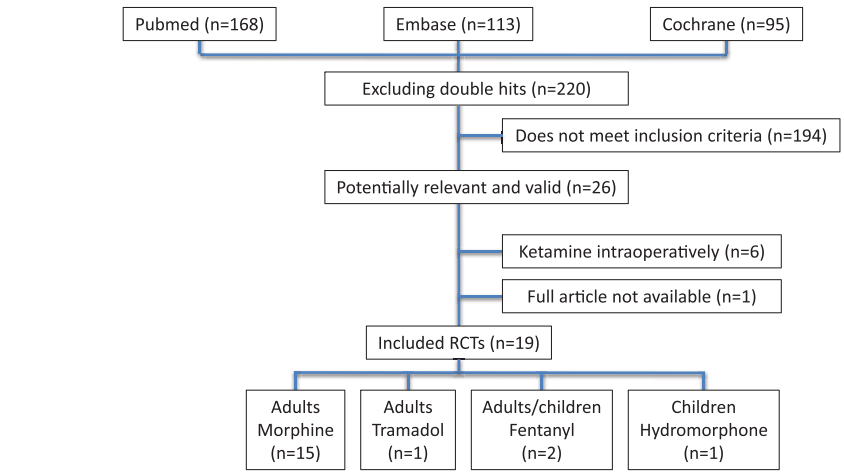

Figure 2. Flowchart describing study selection. PONV, postoperative nausea and vomiting; RCTs, randomized controlled trials.

Table 1

Characteristics of included trials.

Trial (references)	PCA regimen (number of analyzed patients in brackets)	Population	Surgery	Opioid	N	Primary endpoint
Akhavanakbari et al[2]	Morphine 0.2 mg/mL (?) Morphine-ketamine 0.2/1 mg/mL (?)	Adults	Orthopaedic	Morphine	40	Analgesic efficacy
Burstal et al[8]	Morphine 1 mg/mL bolus (33) Morphine-ketamine 1/2 mg/mL bolus (37)	Adults	Gynecology	Morphine	70	Analgesic efficacy and central sensitization
Cha et al[10]	Fentanyl 0.5 $\mu g \cdot kg^{-1} \cdot mL^{-1}$, 1 mL/h + 0.5 mL bolus (30) Fentanyl 0.5 $\mu g \cdot kg^{-1} \cdot mL^{-1}$, 1 mL/h + 0.5 mL bolus; ketamine 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$, 1 mL/h, 0.5 mL bolus (30)	Children	Thoracic	Fentanyl	60	Reduction of opioid consumption
Chazan et al[11]	Morphine 2 mg bolus (22), morphine-ketamine 1/5 mg bolus (24)	Adults	Thoracic	Morphine	46	Analgesic efficacy
Dahi-Taleghani et al[13]	Morphine-placebo 0.5 mg/mL bolus 2 mL (70), morphine-ketamine 0.5/1 mg/mL bolus 2 mL (70)	Adults	Orthopaedic	Morphine	140	Analgesic efficacy
Javery et al[23]	Morphine 1 mg/mL bolus (20), morphine-ketamine 1/1 mg/mL bolus (22)	Adults	Lumbar	Morphine	42	Analgesic efficacy and reduction of opioid side effect
Kamal et al[25]	Morphine 1 mg/mL (40) morphine-ketamine 1/1 mg/mL (40)	Adults	Abdominal	Morphine	80	Reduction of opioid consumption
Kollender et al[29]	Morphine-placebo 1.5 mg bolus (29), morphine-ketamine 1/5 mg bolus (28)	Adults	Tumor, bone, soft tissue	Morphine	57	Reduction of opioid consumption
Lo et al[32]	Morphine 2 mg/mL bolus (15), morphine-ketamine 2/2 mg/mL bolus (15)	Adults	Gynecology	Morphine	30	Analgesic efficacy
Michelet et al[35]	Morphine 1 mg/mL bolus (24), morphine-ketamine 1/1 mg/mL bolus (24)	Adults	Thoracic	Morphine	48	Reduction of opioid consumption
Min et al[36]	Hydromorphone 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (22), hydromorphone 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ + ketamine 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$, background infusion 1 mL/h, bolus 0.5 mL (22)	Children	Thoracic	Hydromorphone	44	Analgesic efficacy
Nesher et al[40]	Morphine-placebo 1.5 mg bolus (29), morphine-ketamine 1/5 mg bolus (28)	Adults	Thoracic	Morphine	57	Analgesic efficacy
Nesher et al[39]	Morphine-placebo 1.5 mg bolus (20), morphine-ketamine 1/5 mg bolus (21)	Adults	Thoracic	Morphine	41	Analgesic efficacy
Reeves et al[43]	Morphine 1 mg/mL bolus (35), morphine-ketamine 1/1 mg/mL bolus (36)	Adults	Abdominal	Morphine	71	Analgesic efficacy
Sami et al[34]	Morphine 0.5 mg/mL, bolus 2 mL (67), morphine-ketamine 0.5/0.5 mg/mL, bolus 2 mL (67)	Adults	Abdominal, gynecology, others	Morphine	134	Analgesic efficacy and reduction of opioid side effect
Sveticic et al[47]	Morphine 1.5 mg bolus (176), morphine-ketamine 1.5/1.5 mg bolus (176)	Adults	Orthopaedic	Morphine	352	Unsatisfactory treatment
Ünlügenç et al[51]	Tramadol 5 mg/mL, background infusion 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$, bolus 0.2 mg/kg (21), tramadol-ketamine 5/1 mg/mL, background infusion 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$, bolus 0.2 mg/kg (22)	Adults	Abdominal	Tramadol	43	Analgesic efficacy
Ünlügenç et al[50]	Morphine 0.4 mg/mL (28), morphine-ketamine 0.4/1 mg/mL (30)	Adults	Abdominal	Morphine	58	Analgesic efficacy
Yeom et al[56]	Fentanyl 1 mL/h, bolus 1 mL, 0.4 $\mu g \cdot kg^{-1} \cdot mL^{-1}$ (20), fentanyl 1 mL/h, bolus 1 mL, 0.4 $\mu g \cdot kg^{-1} \cdot mL^{-1}$; ketamine 30 $\mu g \cdot kg^{-1} \cdot mL^{-1}$ (20)	Adults	Lumbar	Fentanyl	40	Analgesic efficacy

hydromorphone[36] in one each. Ketamine bolus doses ranged from 1 to 5 mg. From the trials that used opioids other than morphine, only the data on pain intensity and opioid-related and ketamine-related adverse effects were analyzed.[10,36,51,56]

Fifteen trials (79%) were properly controlled, ie the opioid regimen was exactly the same in experimental and control groups. In the other 4 trials, all published by the same group of authors,[11,29,39,40] opioid regimens in the experimental groups were

lower compared with the control groups. It remained unclear whether these unequal opioid regimens had been chosen to test the hypothesis that adding ketamine to a reduced dose of an opioid was equally effective as the opioid alone but at a higher dose.

One study was not analyzed because relevant data (pain evaluation, incidence of opioid, or ketamine adverse effect) were reported with unusual scores only and the authors were unable to provide data in a format that could be used for meta-analyses.[32] One study was not analyzed because the authors were unable to provide the number of patients per group.[2] Authors of 1 study confirmed on request that the reported data on morphine consumption had been accidentally inverted in table and text of the published article.[13]

3.3. Synthesis of results

3.3.1. Primary endpoints

3.3.1.1. Pain intensity at 24 hours

Nine trials (535 adults, 60 children) reported pain intensity at rest at 24 hours.[10,11,13,25,29,35,39,43,56] In controls, the median of average pain scores was 3.4 cm (range, 1.9 to 5.7), with ketamine was 2.5 cm (0.8 to 3.6); WMD_{DL} −1.1 cm (98% CI, −1.8 to −0.39), $P < 0.001$ (**Fig. 3**). The data were heterogeneous. No source of heterogeneity could be identified. Trial sequential analysis estimated that, based on our preset criteria, a sample size of 841 was required to reach a definite conclusion of efficacy; therefore, our analysis included only 71% of the required sample size. However, the cumulative Z-curve crossed the 2% O'Brien-Fleming alpha boundaries suggesting that additional trials were unlikely to refute a statistically significant beneficial impact of ketamine on pain intensity at 24 hours.

3.3.1.2. Cumulative morphine consumption at 24 hours

Seven trials (495 adults) reported cumulative morphine consumption at 24 hours.[13,23,25,29,35,40,43] In controls, the median of average morphine consumptions was 46 mg (range, 30 to 71), with ketamine was 24 mg (15 to 77); WMD_{DL} −12.9 mg (98% CI, −22.4 to −3.35), $P = 0.002$ (**Fig. 4**). The data were heterogeneous. No source of heterogeneity could be identified. Trial sequential analysis estimated that, based on our preset criteria, a sample size of 778 was required; therefore, our analysis included 63% only of the required sample size. However, trial sequential analysis suggested that additional trials were unlikely to refute a statistically significant beneficial impact of ketamine on cumulative morphine consumption at 24 hours.

3.3.1.3. Postoperative nausea and vomiting

Seven trials (375 adults, 60 children) reported on the cumulative incidence of a combined PONV outcome.[10,11,29,34,39,40,56] In most trials, the duration of follow-up remained unclear. The proportion of patients with PONV was 44.2% in controls and was 24.7% with ketamine; RR 0.56 (98% CI, 0.40 to 0.78), $P < 0.001$ (**Fig. 5**). The data were homogenous ($P = 0.44$, $I^2 = 0\%$). Trial sequential analysis estimated that, based on our preset criteria, a sample size of 844 was required; therefore, our analysis represented 51.5% only of the required sample size. However, trial sequential analysis suggested that additional trials were unlikely to refute a statistically significant beneficial impact of ketamine on the incidence of PONV.

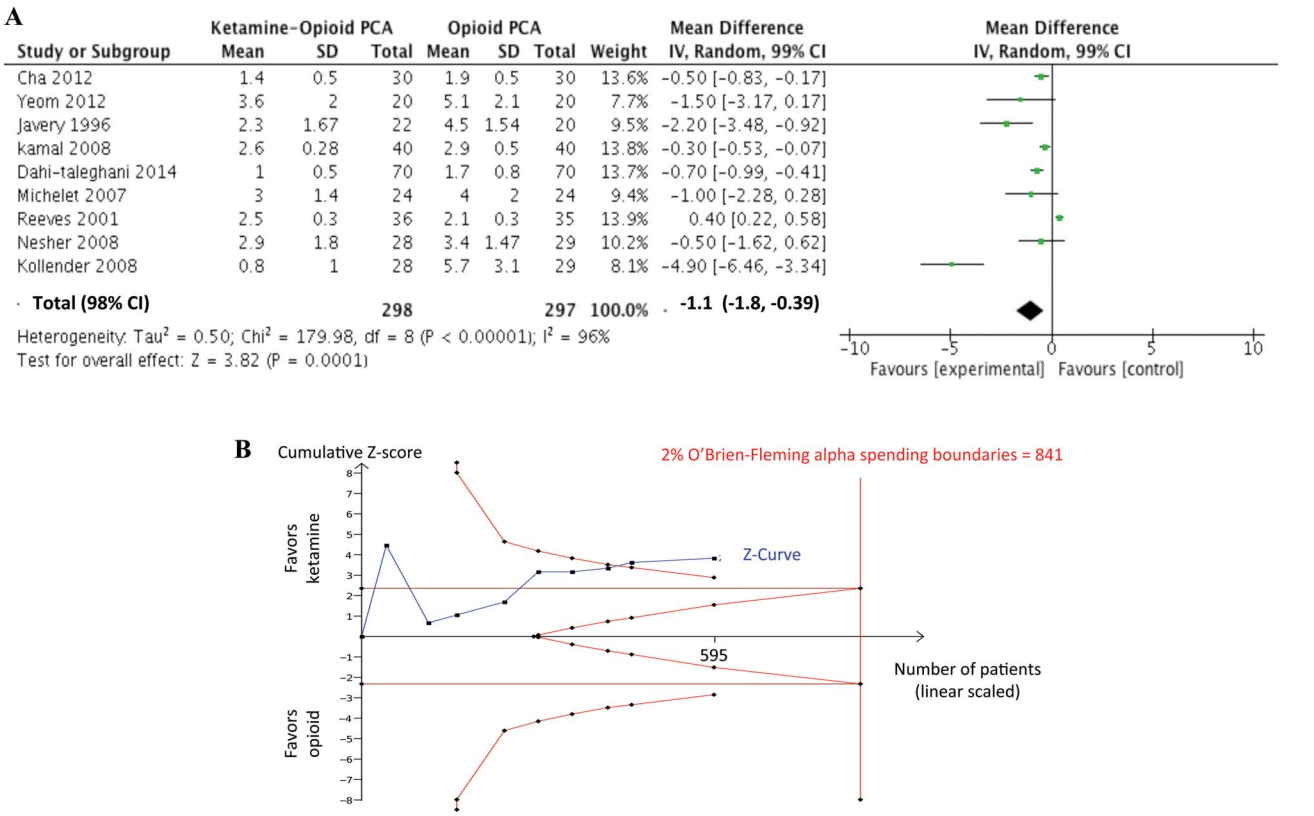

Figure 3. (VAS 0-10 cm) at 24 hours postoperatively. (A) Forest plot (studies classified according to increasing ketamine regimens). (B) Trial sequential analysis. PCA, patient-controlled analgesia; IV, inverse variance.

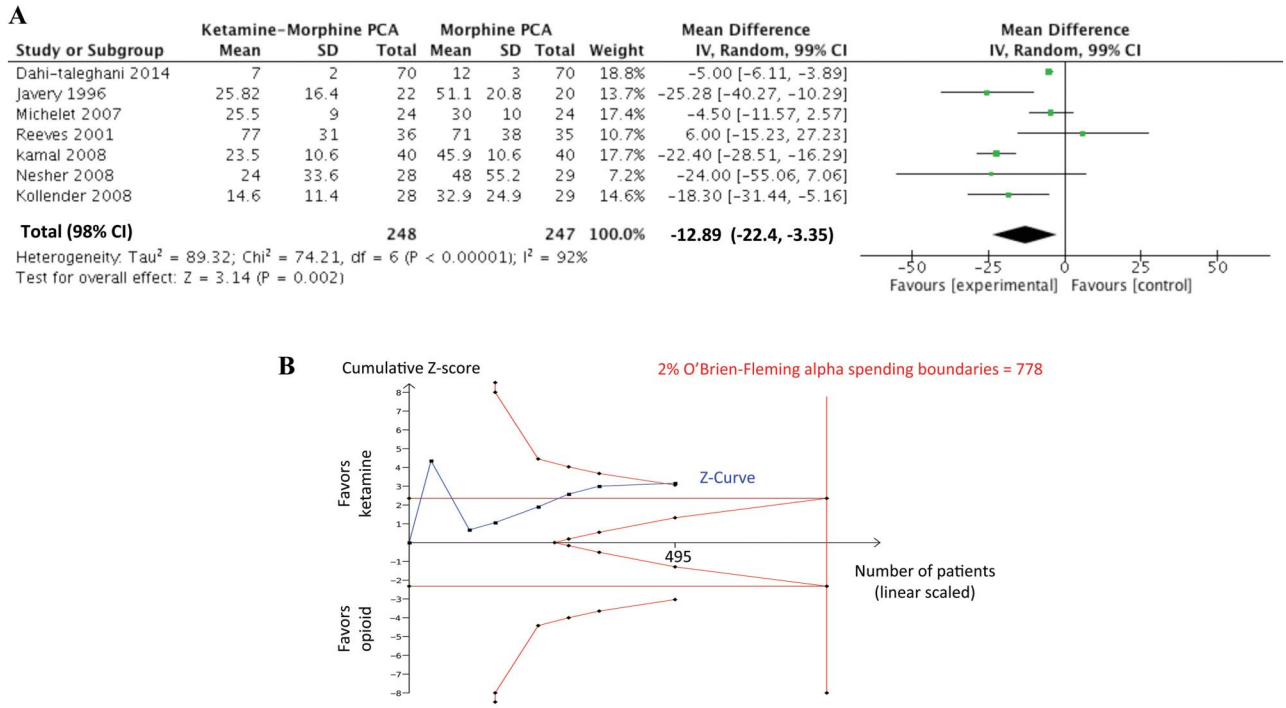

Figure 4. Cumulative morphine consumption at 24 hours postoperatively. (A) Forest plot (studies classified according to increasing ketamine regimens). (B) Trial sequential analysis. IV, inverse variance; PCA, patient-controlled analgesia.

3.3.1.4. Respiratory adverse events

Respiratory adverse events were reported differently across trials. Four trials (235 adults) reported desaturation.[25,29,39,40] Three of those (155 adults) defined desaturation as a pulse oxymetry value <94% with FiO_2 0.4,[29,39,40] and one (80 adults) defined it as a pulse oxymetry value <90%.[25] One trial (48 adults) reported the percentage of time with pulse oxymetry values <90% during the first 3 postoperative nights.[35] Five trials (569 adults, 60 children) searched for symptoms of postoperative respiratory depression.[10,23,34,39,47] Respiratory depression was defined as a respiratory rate <10 min^{-1} or as a pulse oxymetry value <90% at room air,[10] a respiratory rate <10 min^{-1} with a sedation score of 2 on the Ramsey score,[34] or as a respirator rate <8 min^{-1}.[47] Two trials reported respiratory depression without defining it.[23,39]

When all data on respiratory adverse events from 9 studies (811 adults, 60 children) were combined using a random effects model,[10,23,25,29,34,35,39,40,47] the incidence of respiratory adverse events was 9.7% in controls and was 5.5% with ketamine; RR_{DL} 0.31 (98% CI, 0.06 to 1.51), $P = 0.082$ (**Fig. 6**). The data were heterogeneous. No source of heterogeneity could be identified. Trial sequential analysis estimated that, based on our preset criteria, a sample size of 4256 was required; therefore, our analysis included only 20% of the required sample size. Trial sequential analysis indicated that a definite conclusion on respiratory adverse events could not yet be reached.

3.3.1.5. Hallucination

Seven trials (630 adults, 60 children) reported hallucination.[10,25,29,39,40,47,51] Overall, the incidence of hallucination was 4.0% in controls and was 4.6% with ketamine; odds ratios 1.16 (98% CI, 0.47 to 2.79), $P = 0.70$ (**Fig. 7**). The data were homogeneous ($P = 1.0$, $I^2 = 0\%$). Trial sequential analysis estimated that, based on our preset criteria, a sample size of 1114 was required; therefore, our analysis included 62% only of the required sample size. However, trial sequential analysis suggested that further trials were unlikely to reach the conclusion that ketamine doubled the risk of psychotomimetic symptoms. If no continuity correction had been applied, the Z-curve would still have come very close to the futility boundary.

One trial (71 adults) reported a nonsignificant increase in the incidence of vivid dreams with ketamine.[43] Finally, in 1 trial (70 adults), the PCA pump had to be discontinued in 4 patients in the ketamine group because of dysphoria.[8] None of the remaining trials reported psychotomimetic events in either group.

3.3.2. Secondary endpoints

3.3.2.1. Pain intensity at 48 and 72 hours postoperatively

In 7 trials (353 adults, 60 children), patients were using the PCA devices for 48 hours and pain intensity at rest at 48 hours was reported.[10,25,29,35,40,43,56] In 1 trial (46 adults), patients were using the PCA devices for 72 hours, and pain intensity at rest at 72 hours was reported.[11] When these data were combined, the median of the average pain scores in controls was 2.3 cm (range, 1.3 to 4.2), with ketamine was 1.8 cm (0.6 to 2.9); WMD −0.9 cm (95% CI, −1.6 to −0.2) (Appendix: Fig. A, available online at http://links.lww.com/PAIN/A339). The data were heterogeneous. Results became homogenous when data from 4 trials that included patients undergoing thoracic surgery were combined ($P = 0.56$, $I^2 = 0\%$).[10,11,35,40]

3.3.2.2. Cumulative morphine consumption up to 48, 72, and 96 hours

Four trials (230 adults) reported cumulative morphine consumption at 48 hours,[25,35] 72 hours,[11] and 96 hours.[29] In controls, the median of the average morphine consumptions was 67 mg (range, 38 to 84), with ketamine was 45 mg (19 to 66); WMD −17.9 mg

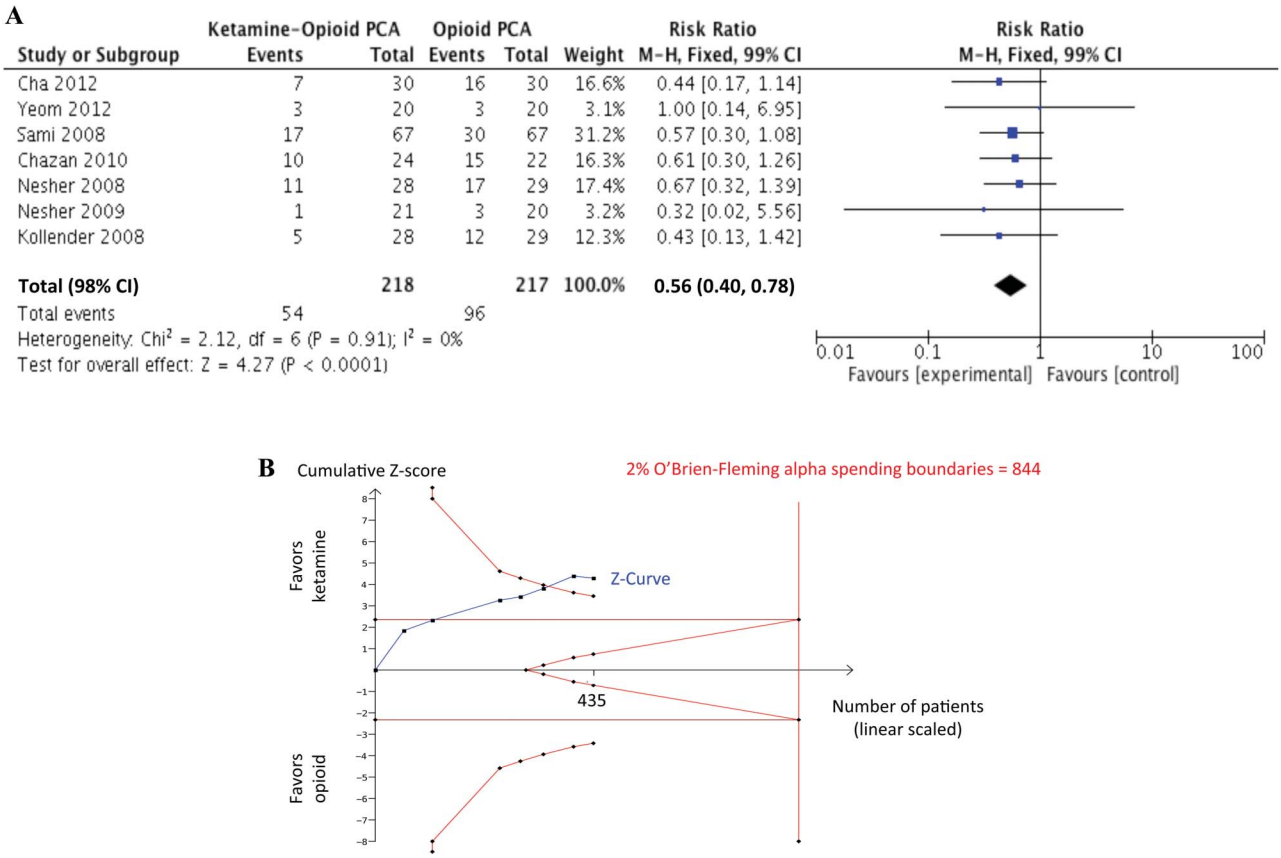

Figure 5. Postoperative nausea and vomiting. (A) Forest plot (studies classified according to increasing ketamine regimens). (B) Trial sequential analysis and M-H, Mantel–Haenszel; PCA, patient-controlled analgesia.

(95% CI, −21.1 to −14.8) (Appendix: Fig. B, available online at http://links.lww.com/PAIN/A339). The data were homogeneous.

3.3.2.3. Analgesic rescue medication

Nine studies (681 adults, 104 children) reported the use of nonopioid analgesics as rescue treatments.[10,11,25,29,35,36,39,40,47] The proportion of patients requiring rescue analgesia was 34.4% in controls and was 27.5% with ketamine; RR 0.72 (95% CI, 0.50 to 1.03), $P = 0.07$ (Appendix: Fig. C, available online at http://links.lww.com/PAIN/A339). The data were heterogeneous. The result became homogenous ($P = 0.18$, $I^2 = 39\%$) when data of 3 trials that were using ketamine boluses of 5 mg were combined.[11,29,40]

3.3.2.4. Nausea

Six trials (743 adults) reported the cumulative incidence of nausea.[8,13,25,47,50,51] Duration of follow-up remained unclear. The proportion of patients with nausea was 35.9% in controls and was 36.5% with ketamine; RR 1.03 (95% CI, 0.87 to 1.22) (Appendix: Fig. D, available online at http://links.lww.com/PAIN/A339). The data were homogenous.

3.3.2.5. Antiemetic use

Six trials (597 adults, 104 children) reported on the use of antiemetic rescue medication.[10,13,35,36,40,47] The proportion of patients requiring antiemetic medication was 34.8% in controls and was 38.9% with ketamine; RR 1.12 (95% CI, 0.93 to 1.34) (Appendix: Fig. E, available online at http://links.lww.com/PAIN/A339). The data were homogenous.

3.3.2.6. Urinary retention

Five trials (354 adults) reported the number of patients needing bladder catheterization.[29,34,35,40,50] The incidence of bladder catheterization was 24.3% in controls and was 16.4% with ketamine; RR 0.69 [95% CI, 0.46 to 1.02] (Appendix: Fig. F, available online at http://links.lww.com/PAIN/A339). The data were homogenous.

3.3.2.7. Pruritus

Seven trials (682 adults, 104 children) reported the incidence of postoperative pruritus.[8,10,11,25,34,36,47] The incidence of pruritus was 19.3% in controls and was 17.8% with ketamine; RR 0.71 [95% CI, 0.34 to 1.46] (Appendix: Fig. G, available online at http://links.lww.com/PAIN/A339). The data were heterogeneous. No source of heterogeneity could be identified.

3.3.3. Dose-responsiveness

There was no graphical evidence of dose-responsiveness. The large variety of ketamine regimens that were used in these trials (**Table 1**) did not allow us to further address this issue.

4. Discussion

4.1. Summary of findings

Our analyses suggest that adding ketamine to an opioid in a PCA device significantly decreases pain intensity and morphine

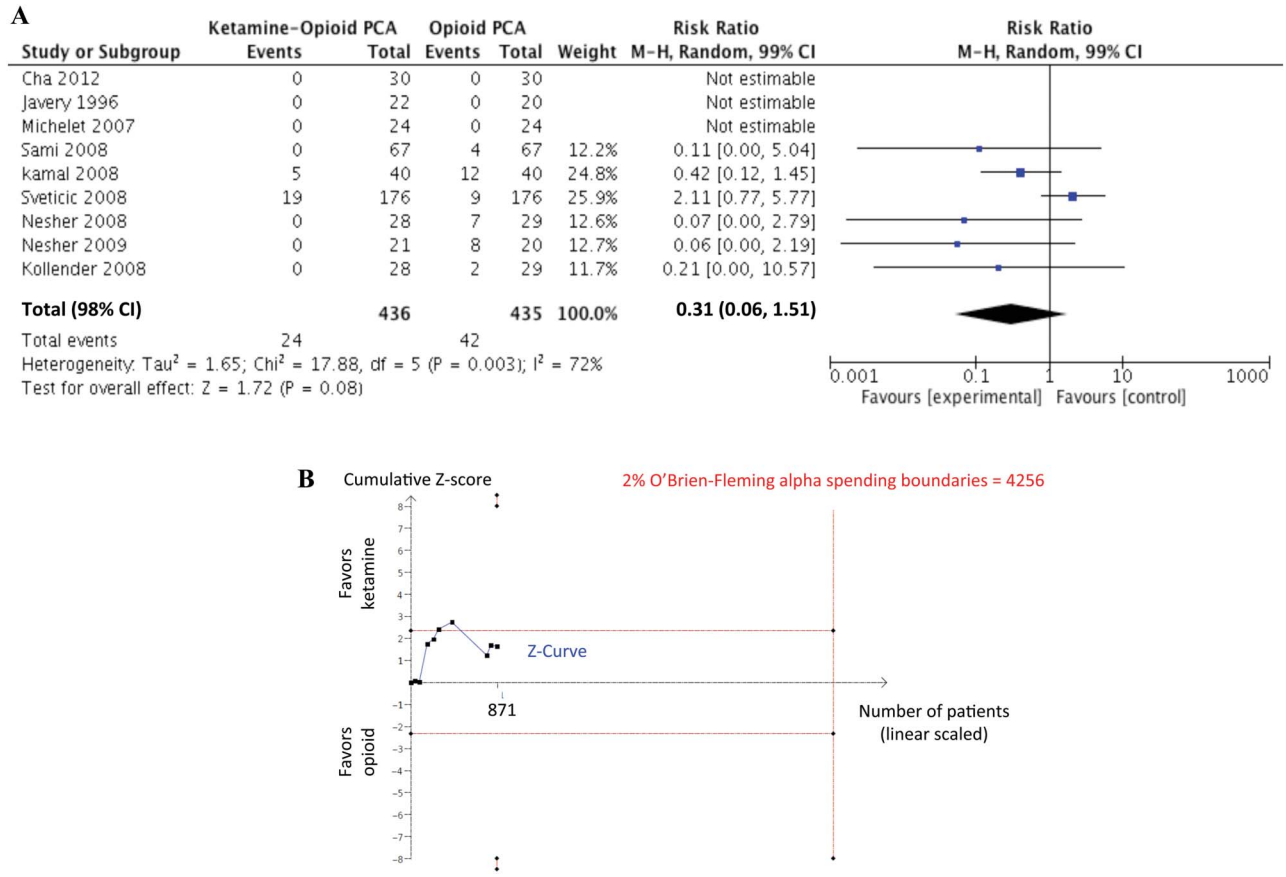

Figure 6. Respiratory adverse events. (A) Forest plot (studies classified according to increasing ketamine regimens). (B) Trial sequential analysis. M-H, Mantel–Haenszel; PCA, patient-controlled analgesia.

consumption 24 hours postoperatively, and the incidence of PONV during hospital stay. Ketamine is unlikely to double the incidence of psychotomimetic adverse effects. Its impact on the incidence of respiratory adverse events remains uncertain.

4.2. What is already known on this subject?

Several systematic reviews have addressed the role of ketamine in surgical patients. Those that tested ketamine added to PCA opioids provided conflicting results. Subramaniam et al. (37 trials, 2385 patients) concluded that ketamine did not improve postoperative analgesia nor increase the incidence of ketamine-related adverse effects.[46] Bell et al (37 trials, 2240 patients) reported significant decreases in cumulative morphine consumption at 24 hours and in the incidence of PONV.[6] Carstensen et al. (11 trials, 887 patients) in a qualitative systematic review, concluded that in patients undergoing thoracic surgery, ketamine decreased pain intensity, cumulative morphine consumption, and postoperative desaturation, whereas in patients undergoing orthopedic or abdominal surgery, the benefit remained unclear.[9] Finally, Wang et al. (36 trials, 2502 patients) concluded that ketamine improved analgesia, and reduced opioid consumption and PONV.[53]

4.3. What does this new analysis add?

Our analysis confirms some previously reported results and adds more information to existing knowledge. Ketamine decreased pain intensity at 24 hours by approximately 1 cm on the 10 cm VAS, and there was some evidence that the analgesic effect was prolonged to 72 hour as long as the patients received the ketamine for that period. Trial sequential analyses confirmed the significant analgesic effect of ketamine although the required sample size to test our hypothesis was not reached. Indirect comparisons with similar analyses testing alternative nonopioid adjuvants suggest that the degree of analgesic efficacy with ketamine is stronger than with acetaminophen[15] or alpha2 agonists,[7] and comparable with nonsteroidal antiinflammatory drugs.[15]

The degree of opioid-sparing at 24 hours after surgery also seemed to be stronger than what has been reported with acetaminophen[15,44] and alpha2 agonists,[7] and comparable with nonsteroidal antiinflammatory drugs.[15] Again, trial sequential analyses confirmed the significant beneficial effect of ketamine, although the required sample size to test our hypothesis was not reached. The clinically relevance of this outcome remains questionable because the average opioid consumption may not be a reliable surrogate of analgesic efficacy.[33,37] However, it is generally admitted that most opioid-related adverse effects are dose-dependent,[54,57] and that their occurrence increases length of hospitalization and costs of care.[5,18,26,54] Moreover, there is growing evidence that opioid-induced hyperalgesia may also be dose-related.[17,19,27] Therefore, the opioid-sparing effect of ketamine may indeed be of clinical relevance. In addition, decreased opioid consumption is likely to be useful in chronic opioid users (for instance, chronic pain patients), and in patients who are sensitive to opioid-related adverse effects (for instance, patients with chronic obstructive pulmonary disease). Finally, patients in

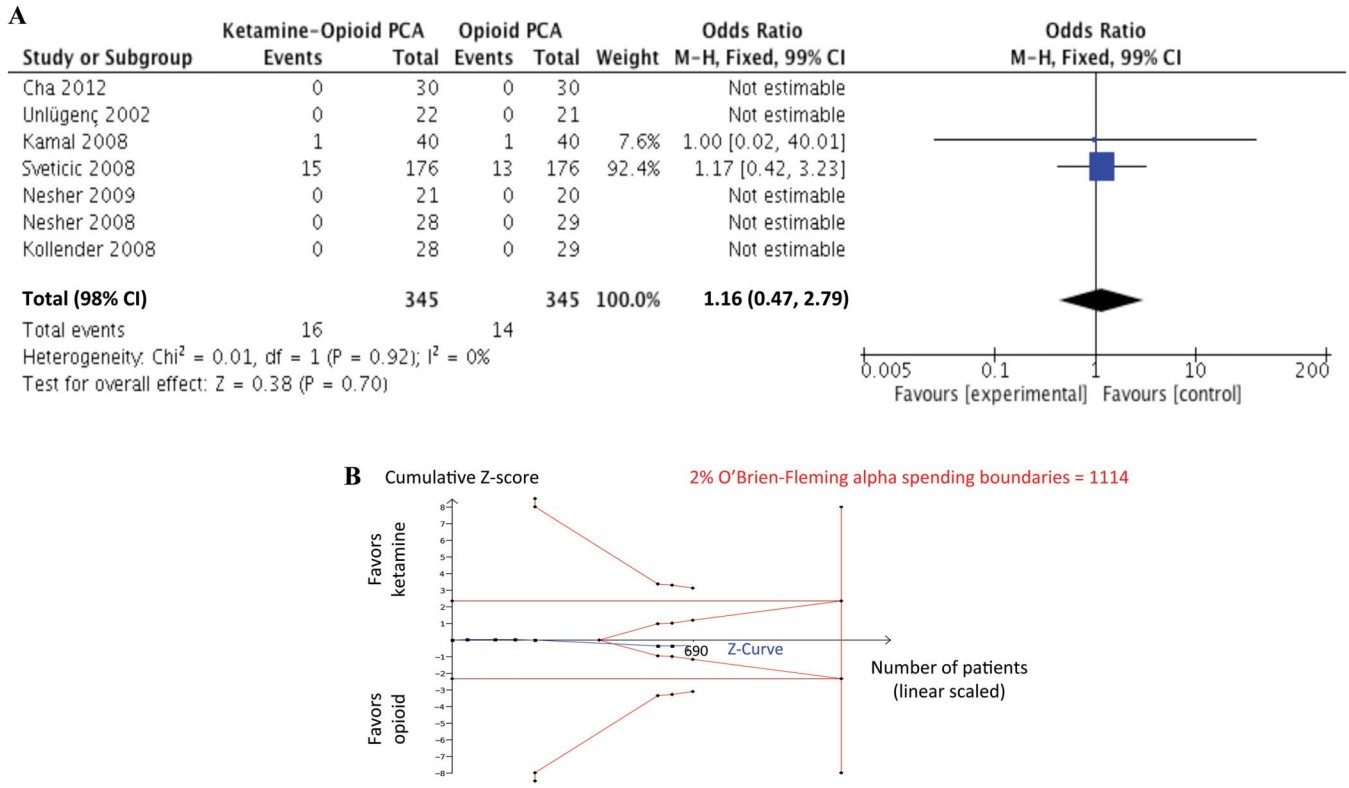

Figure 7. Hallucination. (A) Forest plot (studies classified according to increasing ketamine regimens). (B) Trial sequential analysis. M-H, Mantel–Haenszel; PCA, patient-controlled analgesia.

whom alternative nonopioid adjuvants should be avoided (for instance, nonsteroidal antiinflammatory drugs in renal insufficiency) are also likely to benefit from the addition of ketamine to an opioid PCA.

Postoperative nausea and vomiting is one of the most frequent adverse effects in surgical patients using an opioid PCA device.[52] The average incidence of PONV was significantly decreased with ketamine; the number needed to treat was approximately 5. The impact of ketamine on PONV was reported before.[6,53] A beneficial effect on PONV was also reported with other nonopioid adjuvants that lack a biological basis for a direct antiemetic efficacy such as nonsteroidal antiinflammatory drugs.[15] This supports the hypothesis that the beneficial effect of ketamine on PONV is due to the ketamine-related opioid-sparing rather than to a direct antiemetic effect.

As in previously published similar analyses,[53] we were unable to demonstrate a significant decrease in the incidence of respiratory adverse events with ketamine. Trial sequential analyses suggested that more than 4200 patients were needed to identify a 2-fold decrease in the incidence of respiratory adverse events. Smaller treatment effects would require even larger samples.

Finally, we found no evidence that adding ketamine to an opioid PCA increased the incidence of hallucinations, which remains one of the major concerns of clinicians using this drug. Trial sequential analyses confirmed that ketamine regimens as described in these trials are unlikely to double the risk of hallucination. One study reported unusually high incidences of hallucination in both groups.[47] This may have been due to the definition of that outcome in that study. Unfortunately, the authors were unable to respond to our enquiry. Because the same definition of hallucination was used in all patients, it is unlikely that these high incidences affected the combined analysis. Also, subgroup analysis excluding that study did not change the overall result. However, this observation raises, again, the problem of nonstandardized definitions of outcomes in pain studies. Previous similar analyses did not report either on an increase in psychotomimetic adverse effects with ketamine.[46,53] In 1 analysis, the risk of hallucination was highest in awake or only sedated patients receiving ketamine without a benzodiazepine.[16]

4.4. Strengths and weaknesses of our analysis

Contrary to previous analyses,[6,9,16,46,53] ours was specifically designed to address the impact of adding ketamine to an opioid in an IV PCA. It is also the first using a conservative alpha threshold (2% instead of the conventional 5%) to control for multiple outcome testing. We further used trial sequential analyses to control for multiple testing before the required information size was reached. This allowed us to be more confident regarding our conclusions on the significance of beneficial effects. One problem with trial sequential analyses is that they rely on prehoc baseline hypotheses; not everybody may agree with ours. Specifically, one could argue that doubling the risk of hallucination with ketamine is too large an effect to look for. Interestingly, the required information size was not reached for any of our primary outcomes. Although the trial sequential monitoring boundaries were crossed for some analyses that showed an impact of ketamine that was larger than expected in our prehoc hypotheses, it might be wise to remain cautious when interpreting those results when the information size was not reached. Also, we have performed trial sequential analyses with primary endpoints only.

This systematic review has several limitations. Most of them reside in the methodological weaknesses of the original studies.

First, 9 studies were of small size (less than 50 patients). Although this is in line with many studies included in the anesthesiology literature, it cannot be ignored that small trials have a tendency to overestimate treatment effects. Second, most reported outcomes were not standardized. This illustrates the lack of a common, clearly defined research agenda. Also, some clinically relevant outcomes (for instance, time to transit recovery, urinary retention, and respiratory events) were only inconsistently reported. Third, the opioid-ketamine dose ratio varied widely; all trials testing 5 mg ketamine had been performed by 1 single research group. Dose-responsiveness could not be established. Fourth, we did not search unpublished data and did not use funnel plots to exclude publication bias because none of the outcomes was reported in more than ten studies. Publication bias may have resulted in an overestimation of the beneficial effects of ketamine.

4.5. Research agenda

This systematic review highlights several pharmacological and methodological uncertainties that may be addressed in future trials. For instance, more insight into dose-responsiveness is likely to improve patient care. Patients could be treated with ketamine regimens that are even higher without the risk of adverse drug reactions. Dose-responsiveness may best be tested in randomized trials. Also, long-term outcomes after ketamine PCA treatment, for instance, chronic postoperative pain, should be investigated.

As in similar analyses testing the efficacy of nonopioid adjuvants added to an opioid IV PCA, it remained unclear why pain intensities differed between experimental and control groups although all patients had free access to a PCA device. One would expect that they used the necessary amount of analgesics to achieve an acceptable degree of pain intensity.[33] Reasons why patients receiving ketamine had on average lower pain scores, although they consumed less opioids, should be investigated. This may be due to a synergistic analgesic effect of ketamine and opioid, or because the occurrence of opioid-related adverse effects limited the self-administration of opioids; patients may prefer some degree of pain rather than to suffer from opioid-related adverse effects.

5. Conclusions

In conclusion, there is some evidence that, in the postoperative setting, adding ketamine to an opioid in an IV PCA device has a beneficial effect on analgesia, morphine-sparing, and PONV, and that the risk of hallucination is not increased. The impact on respiratory adverse effect is uncertain. The optimal regimen of ketamine in this setting remains unknown; this should be studied in large randomized dose-finding studies. Future trials should use standardized scales for measurement of pain intensity (for instance, 0-10 cm VAS) and systematically report clinically relevant opioid and ketamine-related adverse effects (respiratory depression, bowel transit recovery, bladder dysfunction, PONV, and psychotomimetic effects).

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A339.

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References

[1] Abreu M, Aguado D, Benito J, García-Fernández J, Gómez de Segura IA. Tramadol-induced hyperalgesia and its prevention by ketamine in rats. Eur J Anaesthesiol 2015;32:735–41.
[2] Akhavanakbari G, Mohamadian A, Entezariasl M. Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery. Perspect Clin Res 2014;5:85–7.
[3] Aubrun F, Gaillat C, Rosenthal D, Dupuis M, Mottet P, Marchetti F, Coriat P, Riou B. Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. Eur J Anaesthesiol 2008;25:97–105.
[4] Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angeillillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized controlled trials. J Clin Anesth 1993;5:182–93.
[5] Barletta JF, Asgeirsson T, Senagore AJ. Influence of intravenous opioid dose on postoperative ileus. Ann Pharmacother 2011;45:916–23.
[6] Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;25:CD004603.
[7] Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Article Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012;116:1312–22.
[8] Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care 2001;29:246–51.
[9] Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 2010;104:401–6.
[10] Cha MH, Eom JH, Lee YS, Kim WY, Park YC, Min SH, Kim JH. Benefical effects of adding ketamine to intravenous patient-controlled-analgesia with fentanyl after the nuss procedure in pediatric patients. Yonsei Med J 2012;53:427–32.
[11] Chazan S, Buda I, Nesher N, Paz J, Weinbroum A. Low-dose ketamine via intravenous patient-controlled analgesia device after various transthoracic procedures improves analgesia and patient and family satisfaction. Pain Manag Nurs 2010;11:169–76.
[12] Colwell CW, Morris BA. Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopedic procedure. J Bone Joint Surg Am 1995;77:726–33.
[13] Dahi-Taleghani M, Fazli B, Ghasemi M, Vosoughian M, Dabbagh A. Effect of intravenous patient controlled ketamine analgesia on postoperative pain in opium abusers. Anesth pain Med 2014;4:e14129.
[14] Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management : evidence from published data. Br J Anaesth 2002;89:409–23.
[15] Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103:1296–1304.
[16] Elia N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. PAIN 2005;113:61–70.
[17] Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 2014;112:991–1004.

[18] Gan TJ, Robinson SB, Oderda GM, Scranton R, Pepin J, Ramamoorthy S. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. Curr Med Res Opin 2015;31:677–86.
[19] Grosu I, de Kock M. New concepts in acute pain management: strategies to prevent chronic postsurgical pain, opioid-induced hyperalgesia, and outcome measures. Anesthesiol Clin 2011;29:311–27.
[20] Hercock T, Gillham MJ, Sleigh J, Jones SF. The addition of ketamine to patient controlled morphine analgesia does not improve quality of analgesia after total abdominal hysterectomy. Acute Pain 1999;2:68–72.
[21] Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[22] Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006:CD003348.
[23] Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996;43:212–5.
[24] Jensen LL, Handberg G, Helbo-Hansen HS, Skaarup I, Lohse T, Munk T, Lund N. No morphine sparing effect of ketamine added to morphine for patient-controlled intravenous analgesia after uterine artery embolization. Acta Anaesthesiol Scand 2008;52:479–86.
[25] Kamal HM. Ketamine as an adjuvant to morphine for patient controlled analgesia in morbidly obese patients. J Med Sci 2008;8:364–70.
[26] Kane-Gill SL, Rubin EC, Smithburger PL, Buckley MS, Dasta JF. The cost of opioid-related adverse drug events. J Pain Palliat Care Pharmacother 2014;28:282–93.
[27] Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: Systematic review. Front Pharmacol 2014;5:108.
[28] Kissin I, Bright CA, Bradley EL. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anesth Analg 2000;91: 1483–8.
[29] Kollender Y, Bickels J, Stocki D, Maruoani N, Chazan S, Nirkin A, Meller I, Weinbroum A. Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. Eur J Cancer 2008;44:954–62.
[30] Laulin J-P, Maurette P, Corcuff J-B, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg 2002;94:1263–9.
[31] Lebovits AH, Zenetos P, O'Neill DK, Cox D, Dubois MY, Jansen LA, Turndorf H. Satisfaction with epidural and intravenous patient- controlled analgesia. Pain Med 2001;2:280–6.
[32] Lo A, Macpherson N, Spiwak R. Prospective randomized trial of patient-controlled analgesia with ketamine and morphine or morphine alone after hysterectomy. Can J Hosp Pharm 2008;61:334–9.
[33] McQuay HJ, Poon KH, Derry S, Moore RA. Acute pain: combination treatments and how we measure their efficacy. Br J Anaesth 2008;101:69–76.
[34] Mebazaa S, Mestiri T, Kaabi B, Ben Ammar MS. Clinical benefits related to the combination of ketamine with morphine for patient controlled analgesia after major abdominal surgery. Tunis Med 2008;86:435–40.
[35] Michelet P, Guervilly C, Hélaine A, Avaro JP, Blayac D, Gaillat F, Dantin T, Thomas P, Kerbaul F. Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. Br J Anaesth 2007;99: 396–403.
[36] Min TJ, Kim WY, Jeong WJ, Choi JH, Lee YS, Kim JH, Park YC. Effect of ketamine on intravenous patient-controlled analgesia using hydromorphone and ketorolac after the nuss surgery in pediatric patients. Korean J Anesthesiol 2012;62:142–7.
[37] Moore R, Mhuircheartaigh R, Derry S, McQuay H. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. Eur J Anaesthesiol 2011;28:427–32.
[38] Murdoch CJ, Crooks BA, Miller CD. Effect of the addition of ketamine to morphine in patient-controlled analgesia. Anaesthesia 2002;57:484–8.
[39] Nesher N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum A. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. Chest 2009;136:245–52.
[40] Nesher N, Serovian I, Marouani N, Chazan S, Weinbroum A. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. Pharmacol Res 2008;58:38–44.
[41] Pacreu S, Fernández Candil J, Moltó L, Carazo J, Fernández Galinski S. The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. Acta Anaesthesiol Scand 2012;56:1250–6.
[42] Park SJ, Song JW, Shim JK, Song Y, Kwak YL, Yang SY. Effect of ketamine as an adjunct to intravenous patientcontrolled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. Br J Anaesth 2013;111:630–5.
[43] Reeves M, Lindholm DE, Myles PS, Fletcher H, Hunt JO. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesth Analg 2001;93:116–20.
[44] Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005;94:505–13.
[45] Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997:1124–32.
[46] Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004;99:482–95.
[47] Sveticic G, Farzanegan F, Zmoos P, Zmoos S, Eichenberger U, Curatolo M. Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? Anesth Analg 2008;106:287–93.
[48] Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen: Denmark Copenhagen Trial Unit, Cent. Clin. Interv. Res, 2011. Available at: www.ctu.dk/tsa.
[49] Trujillo KA, Akil H. Inhibition of opiate tolerance by non-competitive N-methyl-D-aspartate receptor antagonists. Brain Res 1994;633:178–88.
[50] Unlügenç H, Ozalevli M, Güler T, Isik G. Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. Eur J Anaesthesiol 2003;20:416–21.
[51] Unlügenç H, Gündüz M, Ozalevli M, Akman H. A comparative study on the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery. Acta Anaesthesiol Scand 2002;46:1025–30.
[52] Walder B, Schafer M, Henzi I, Tramèr MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiol Scand 2001;45:795–804.
[53] Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anesth 2015:1–15.
[54] Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002;3:159–80.
[55] Wu YQ, Li H, Xiong JC, Xu ZM, Ma LY, Huang XM, Zhang DT, Feng J. Effects of patient-controlled analgesia with small dose ketamine combined with morphine and the influence thereof on plasma beta-endorphin level in patients after radical operation for esophageal carcinoma [in chinese]. Zhonghua Yi Xue Za Zhi 2009:314–7.
[56] Yeom JH, Chon MS, Jeon WJ, Shim JH. Peri-operative ketamine with the ambulatory elastometric infusion pump as an adjuvant to manage acute postoperative pain after spinal fusion in adults: a prospective randomized trial. Korean J Anesthesiol 2012;63:54–8.
[57] Zhao SZ, Chung F, Hanna DB, Raymundo AL, Cheung RY, Chen C. Dose-response relationship between opioid use and adverse effects after ambulatory surgery. J Pain Symptom Manage 2004;28:35–46.