

Original Article

Morphine with adjuvant ketamine versus higher dose of morphine alone for acute pain: a meta-analysis

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Abstract: Purpose: Ketamine is currently the N-methyl-D-aspartate receptor channel blocker in clinical use. Morphine in pain management is usually limited by adverse effect such as nausea and vomiting. Adjuvant treatment with ketamine may be value in giving better analgesia with fewer adverse effects. The purpose of this meta-analysis was to evaluate the differences when patients received morphine with adjuvant ketamine (MK) compared with higher dose of morphine (MO) for acute pain. Methods: The PubMed, EMBASE and the Cochrane Library databases were searched (Last search performed on July 1, 2014) by two reviewers independently. Data were extracted independently by the same two individuals who searched the studies. Results: A total of 7 trials involving 492 patients were included in the current analysis. We found pain scores were lower in the MK group compared to the MO group [MD 2.19, 95% CI (1.24, 3.13) $P < 0.00001$]. And more patients in the MO required diclofenac [OR 1.97, 95% CI (1.06, 3.67) $P = 0.03$]. Furthermore, morphine plus ketamine can reduced post-operative nausea and vomiting (PONV) [OR 3.71, 95% CI (2.37, 5.80) $P < 0.00001$]. Importantly, the wakefulness scores for the MK group were consistently and significantly better than those for the MO group [MD -1.53, 95% CI (-2.67, -0.40) $P = 0.008$]. Conclusion: The use of ketamine plus 1/4~2/3 the dose of morphine is better than higher dose of morphine alone in reducing pain scores, and rescuing analgesic requirement. It also improved PONV and wakefulness.

Keywords: Morphine, ketamine, acute pain, meta-analysis

Introduction

Acute pain is not satisfactory controlled despite the administration of morphine in clinical. The administration of large amounts of morphine to the awakening patient may cause respiratory and hemodynamic depression [1, 2]. Also, higher dose of morphine can cause serious nausea and vomiting. Recent research indicates that morphine not only analgesia, but also hyperalgesia [3]. Consequently, perioperative morphine may increase postoperative pain and requirement [4]. For these reasons, supplementation of morphine with adjuvant agents may be a preferred way of effective controlling pain while reducing the incidence of adverse events [5, 6].

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist was shown to enhance opioid-induced antinociception [7], to

reduce hyperalgesia and when combined with morphine to lower morphine consumption [8]. But, the role of opioid mechanisms in ketamine analgesia in man is still undecided [9]. Anti-inflammatory effects of ketamine have been consistently reported in recent years [10, 11]. Ketamine can release adenosine leading to inhibition of proinflammatory cytokine secretion. This antiinflammation effect might play a role in pain conditions. Thus, we hypothesize that morphine with adjuvant ketamine (MK) is better in reducing pain scores, rescuing analgesic requirement and improving PONV and wakefulness when compared with higher dose of morphine alone (MO).

Methods

Search strategy

We identified randomized controlled trials (RCTs) by electronically searching the following da-

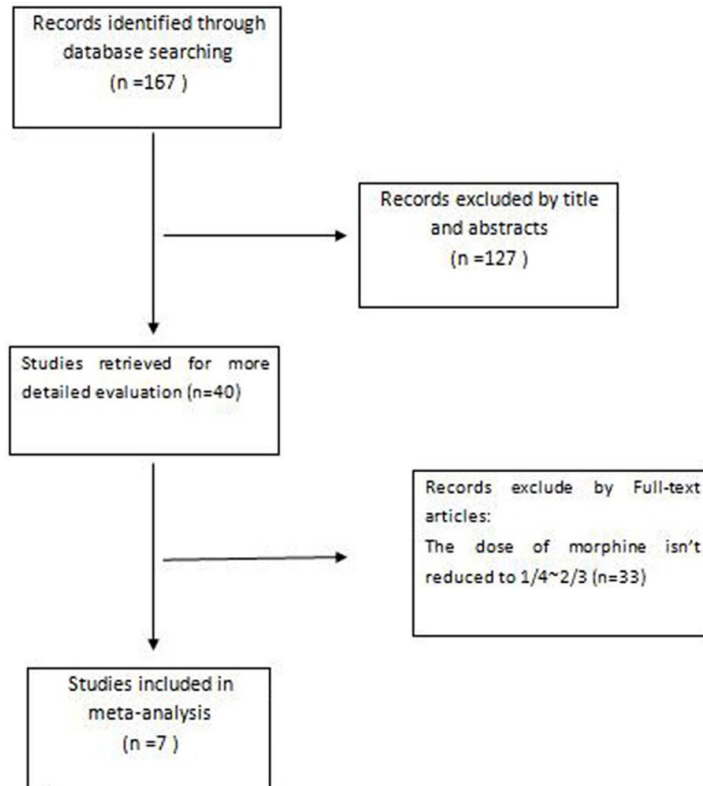


Figure 1. Flow chart of the study selection procedure.

tabase: PubMed, EMBASE and the Cochrane Library. Briefly, the following medical subject headings (MeSH) were included: morphine, ketamine, human and randomized controlled trial, the last search performed on July 1, 2014. Alternative spellings were considered when searching. We removed duplicates that were identified in multiple database searches.

Inclusion criteria

Randomized controlled trials (RCTs) that compared morphine plus ketamine with morphine alone for acute pain were included. The dose of morphine must be reduced to 1/4~2/3 in MK group when compared with that of MO group. English language but no publication date limits were set.

Selection of studies

Two reviewers (Xibing DING, Shuqing JIN) used the pre-specified criteria to screen for relevant titles, abstracts and full papers. An article was removed if it was determined not meet the inclusion criteria. If these two reviewers reached different final selection decisions, a third reviewer (Quan Li) was consulted.

Data extraction

We extracted the following data from the included articles: First author name, publication date, number of patients, study design, description of interventions between MK group and MO group, pain scores (Visual Analogue Scale), wakefulness scores (Visual Analogue Scale), number of PONV and number of diclofenac. The above definition of indicators is in accordance with the definition of the original. These data were then compiled into a standard table. The two reviewers (Xibing Ding, Shuqing Jin) who selected the appropriate studies also extracted the data and evaluated the risk of bias. It was necessary to consult an arbiter (Quan Li) to reconcile any disagreement.

Assessing the risk of bias

We used the Cochrane Handbook V5.0.2 [12] to assess the risk of bias for all articles. The following information was evaluated: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. Two reviewers (Xiaoyin Niu, Ting-ting Wang) evaluated the methodological quality of all articles examined in the current study. An arbiter (Quan Li) was consulted to reconcile any disagreements.

Statistical analysis

Review Manager Software (Revman 5.0, The Cochrane Collaboration, Oxford, United Kingdom) was used for the meta-analysis. Heterogeneity among the studies was evaluated using I^2 statistic and chi-squared test. The fixed effects model was used if the heterogeneity test did not reveal statistical significance ($I^2 < 50\%$; $P > 0.1$). Otherwise, we adopted the random effects model. The variables of pain scores and wakefulness in the studies included in this meta-analysis were continuous, so we used the mean difference (MD) and 95% confidence interval (95% CI). Other variables, such as No. of PONV and diclofenac were dichotomous data, so we used the Odds Ratio (OR) and 95% CI. All tests of statistical significance were two-sided [13].

Ketamine for acute pain

Table 1. Characteristics of included studies

Article	Year	No. of patients	MK Group	MO Group
Weinbroum AA	2003	245	15 µg/kg of morphine plus 250 µg/kg of ketamine intravenously	30 µg/kg of morphine plus saline intravenously
Arroyo-Novoa CM	2011	22	50 µg/kg of morphine plus ketamine 250 µg/kg intravenously	100 µg/kg of morphine plus saline intravenously
Wong CS	1996	20	0.5 mg morphine plus 10.0 mg ketamine epidural catheter	2.0 mg morphine epidural catheter
Nesher N	2008	58	1.0 mg morphine plus 5.0 mg ketamine by IV-PCA	1.5 mg bolus by IV-PCA
Chazan S	2010	46	1.0 mg morphine plus 5.0 mg ketamine/bolus by PCA	2.0 mg/bolus morphine by PCA
Nesher N	2009	41	1.0 mg morphine plus 5.0 mg ketamine/bolus by IV-PCA	1.5 mg morphine plus saline by IV-PCA
Kollender Y	2008	60	1.0 mg morphine plus 5.0 mg ketamine/bolus by IV-PCA	1.5 mg morphine/bolus by IV-PCA

MK: morphine plus ketamine; MO: morphine alone.

Table 2. Risk of bias assessment of included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arroyo-Novoa CM 2011	+	?	-	-	+	+	-
Chazan S 2010	+	+	+	+	+	+	-
Kollender Y 2008	+	?	+	+	+	+	-
Nesher N 2008	+	?	+	+	+	+	-
Nesher N 2009	+	?	+	+	+	+	-
Weinbroum AA 2003	+	?	+	+	+	+	-
Wong CS 1996	+	?	+	+	+	+	-

potentially eligible articles, only 7 articles fulfilled the inclusion criteria [14-20]. The remaining 33 articles were removed because the dose of morphine didn't reduced to 1/4~2/3 in MK group when compared with that of MO group. A detailed explanation of the full electronic search strategy for PubMed is presented in **Figure 1**. Among these the dose of morphine and ketamine are not the same in each paper. The characteristics of each included study are described in **Table 1**.

Risk of bias of included studies

According to the Cochrane Handbook V5.0.2, each article was at a high risk of bias. Thus, the evidence involved in this meta-analysis had a high overall risk of bias. Each article was described as randomized. Only 1 article used the allocation concealment method. Most articles were blinded except 1. Incomplete outcome data were at a low risk of bias in all articles. Selecting reporting bias was considered low for with no access to each trial's original protocol. The risk of bias assessment of all included studies is described in **Table 2**.

The primary outcomes: MK versus MO on the analgesic efficacy

Trials assessed pain intensity using a visual analog scale. There was statistically significant difference in pain scores at 24h between MK group and MO group [MD (2.19), 95% CI (1.24, 3.13), $P < 0.00001$] (**Figure 2**). If pain was not attenuated within 30 min of initial activation, a rescue dose of diclofenac 75 mg was available in four articles. Significant difference in No. of diclofenac was observed between the two groups. [MD (1.97), 95% CI (1.06, 3.67),

Results

Search results

The process of indentifying eligible studies was outlined in **Figure 1**. 167 records were initially identified through the PubMed, Embase and the Cochrane Library. Of these, 40 potentially eligible articles were included based on their titles and abstracts. After reviewing these 40

Ketamine for acute pain

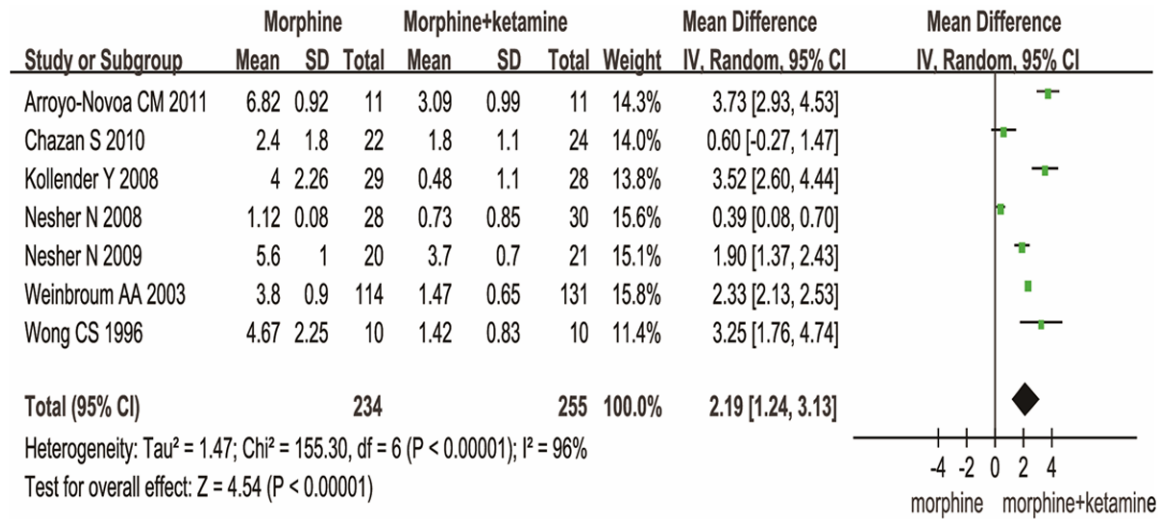


Figure 2. MK versus MO on the pain scores.

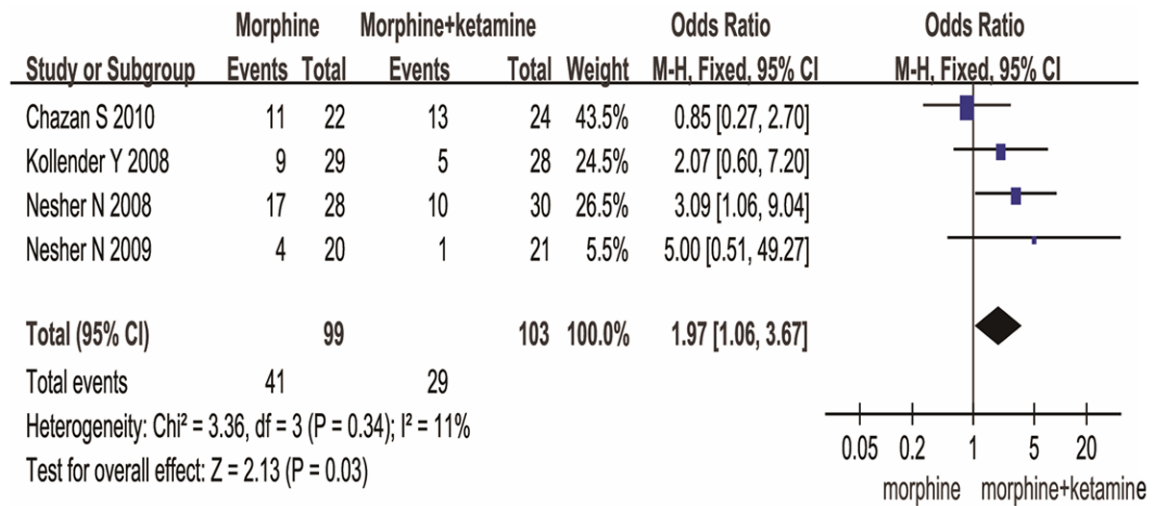


Figure 3. MK versus MO on the No. of diclofenac.

P=0.03] (Figure 3). These data show MK group is better than MO group in reducing pain scores, rescuing analgesic requirement.

The secondary outcomes: MK versus MO on the side effects

The side effects consist of wakefulness and PONV. Compared to MO group, MK group resulted in a significant difference in wakefulness [MD (-1.53), 95% CI (-2.67, -0.40), P=0.008] (Figure 4) and PONV [OR (3.71), 95% CI (2.37, 5.80), P<0.00001] (Figure 5). These data show MK is better than MO group in side effects.

Discussion

To our knowledge, this is the first meta-analysis to evaluate the effect of ketamine plus low dose of morphine for acute pain. In this study, a small dose of ketamine with morphine not only reduced pain intensity but also improved wakefulness and PONV when compared with the higher dose of morphine alone.

This finding suggests that the combination of ketamine with morphine results in synergistic effects. These effects may be related to the different mechanisms [9]. Ketamine may produce antinociception through various mechanisms

Ketamine for acute pain

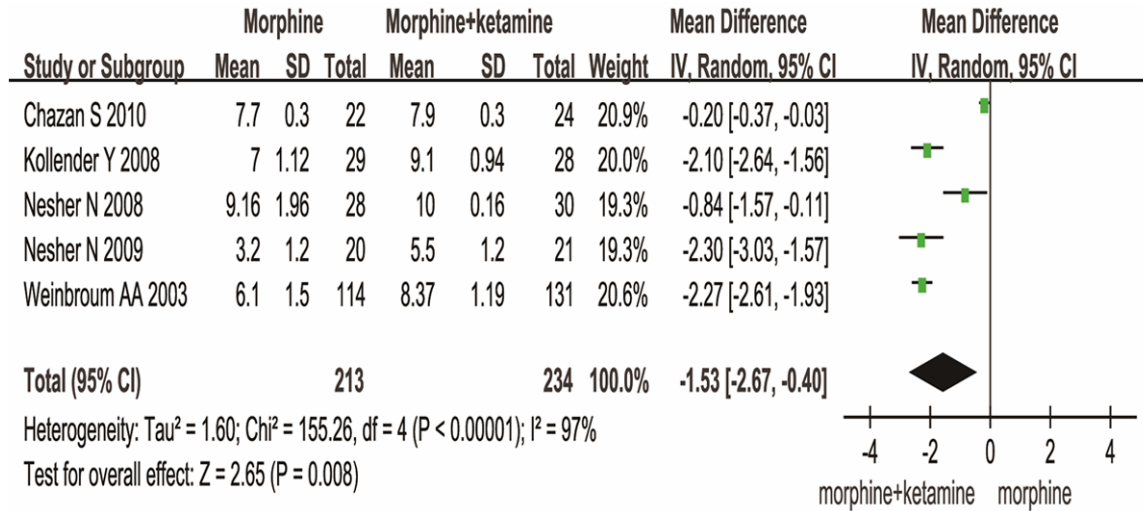


Figure 4. MK versus MO on the wakefulness.

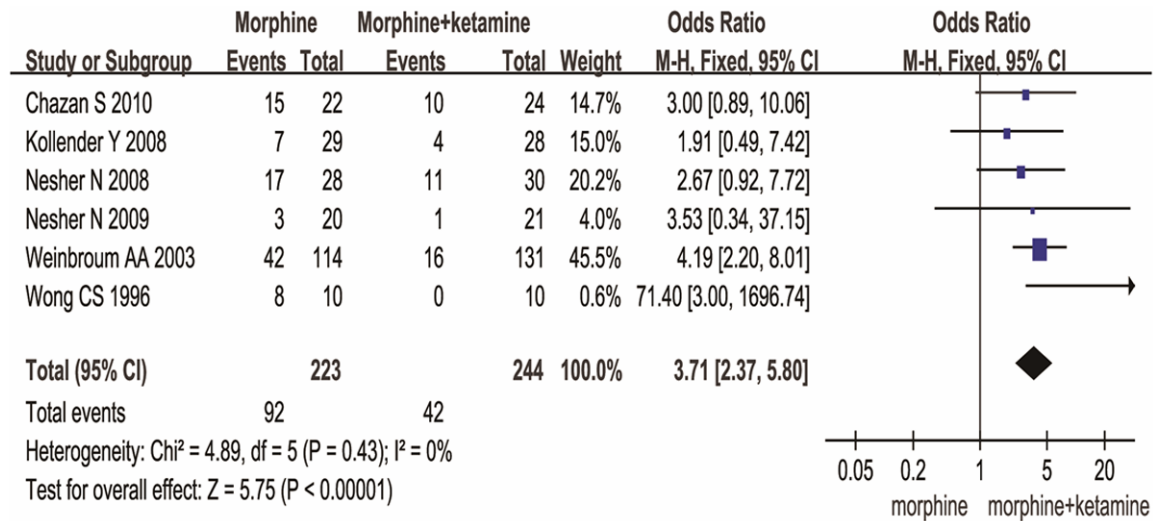


Figure 5. MK versus MO on PONV.

of action: interaction with μ -receptors, NMDA receptor antagonism and activation of the descending pain inhibitory monoaminergic pathway [21]. Morphine and other opioids produce antinociception through μ -receptor agonist activity, they also activate NMDA receptors, resulting in hyperalgesia and the development of tolerance to opioids [22]. Thus, if this was the type of tolerance or resistance involved in the sustained and severe acute pain in patients, it could be overcome by small dose of ketamine either via central desensitization or via antagonization of NMDA activity [18].

Although our study shows MK group is better in reducing pain scores, rescuing analgesic

requirement and improving PONV, wakefulness, it doesn't mean there are no disadvantages of ketamine. Ketamine has been recognized as a potent psychedelic drug and dissociative anesthetic since its introduction into clinical practice [23]. It provokes imaginative, dissociative states, and psychotic symptoms up to schizophrenia due to its NMDA-antagonistic action [24-26] as well as severely impairing semantic and episodic memory when used in sub-anesthetic doses [26]. A dissociative effect of loss-of-self, inability to move the body, and isolation of mind from body is reported when ketamine is used as analgesic. Ketamine can cause emergence phenomena that have been variously described as a floating

sensation, vivid pleasant dreams, nightmares, hallucinations and delirium [23]. Arroyo-Novoa CM et al. [14] reported 91 percent (n=10) of patients who had received MK had adverse effects compared with 0% of the patients when they were treated with MO. The most common adverse effects were hallucinations (n=4, 36%) and strange sensations (n=6, 55%). But Neshar N et al. [20] reported no patient in MK group had illusions or bad dreams. The reason most likely is the small intermittent dosing of ketamine. Weinbroum AA et al. [18] also concluded a similar result, at no time did patients report hallucinations; but 1 patient described an unpleasant dream.

Ketamine provides profound analgesia after neuraxial application, which has triggered great interest in its potential benefits during neuraxial anesthesia. However, the widespread use of ketamine has been hampered due to fear of potential neurotoxicity [27]. Neurotoxicity was reported in a patient after long-term intrathecal administration of ketamine with preserves due to chronic pain [28]. But in a recent clinical study with 24 infants concluded that there was no convincing evidence that ketamine was neurotoxic [29].

Limitation

This meta-analysis was characterized by several limitations that should be noted. Firstly, which is common in many systematic reviews, was that the findings were based on relatively low quality data that had a high risk of bias. Also the included papers just come from that written by English language. Secondly, the sample sizes of these studies were small which may lead to a small-study effect, thus we should be cautious of the application of this meta-analysis. Thirdly, we did not study the hallucinations, strange sensations and haemodynamic alterations because we can't get enough data. At last, there were high levels of heterogeneity when evaluating the pain scores and wakefulness most likely to due to different dose of morphine and ketamine, also the different in route of drug administration and anesthesia. Most papers used the intravenous route, but Wong CS et al. [19] used the epidural catheter especially. Of course, the most influence came from the surgical procedures, because the type of surgery made a difference in the severity of pain.

Conclusions

Our analysis represents a least-biased attempt to pool the results of several studies. Larger, prospective, randomized trials which compared morphine plus ketamine and morphine are necessary to confirm these findings.

In summary, this meta-analysis showed the use of ketamine plus 1/4~2/3 the dose of morphine is better than higher dose of morphine alone in reducing pain scores, rescuing analgesic requirement. It also improved PONV and wakefulness.

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Disclosure of conflict of interest

None.

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Ketamine for acute pain

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