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Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials

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Abstract

Study Design—Meta-analysis of randomized controlled trials.

Objective—To evaluate the effectiveness of perioperative supplemental ketamine to reduce postoperative opioid analgesic consumption following spine surgery.

Summary of Background Data—Although low-dose supplemental ketamine has been known to reduce pain after surgery, there is conflicting evidence regarding whether ketamine can be effective to reduce opioid consumption following spine surgery.

Methods—Comprehensive search of PubMed, the Cochrane Central Register of Controlled Trials for prospective randomized controlled trials (RCTs), Web of Science, and Scopus. Patients that received supplemental ketamine were compared to the control group in terms of postoperative morphine equivalent consumption, pain scores, and adverse events. Mean differences (MD) and 95% confidence intervals (CI) were used to describe continuous outcomes. Odds Ratios (OR) and 95% CIs were applied to dichotomous outcomes.

Results—A total of 14 RCTs comprising 649 patients were selected for inclusion into the meta-analysis. Patients that were administered adjunctive ketamine exhibited less cumulative morphine equivalent consumption at 4, 8, 12, and 24 hours following spine surgery (all ps<0.05). The ketamine group also reported lower postoperative pain scores at 6, 12, and 24 hours (all ps<0.05). None of the adverse events studied attained statistical significance (all ps>0.05).

Conclusions—Supplemental perioperative ketamine reduces postoperative opioid consumption up to 24 hours following spine surgery.

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Conflicts of Interest: None.

Device Status/Drug Statement:

- The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

Level of Evidence—1

Keywords

ketamine; analgesic; analgesia; spine surgery; postoperative pain; complication; meta-analysis; randomized controlled trial

INTRODUCTION

Ketamine is a commonly used anesthetic agent that binds N-methyl-d-aspartate receptors (NMDAR) in addition to several opioid receptors (μ, δ, and κ)[1–2]. In addition, supplemental low-dose ketamine can be used for analgesia[3]. In general, adjuvant perioperative ketamine has been reported to reduce morphine consumption in the first 24 hours following surgery with little to no adverse events[4]. Vague feelings, blurred vision, and hallucinations are the adverse events most commonly encountered[1]. Ketamine may be administered as a single dose, continuous intravenous (IV) infusion, intravenous patient-controlled analgesia (IV-PCA), or epidural infusion[2]. It may be administered preoperatively, intraoperatively, and/or postoperatively[1]. Although supplemental ketamine has been studied broadly in a variety of procedures and operations, there is no consensus regarding the effectiveness of adjunctive ketamine analgesic use specifically in spine surgery. Thus, the primary objective of this study was to determine whether perioperative low-dose ketamine reduced opioid consumption after spine surgery. Secondary goals included determining if ketamine use affected postoperative pain scores and if administration of ketamine was linked to higher rates of complications.

MATERIALS AND METHODS

Systematic Search

A systematic search strategy was designed and tailored to each database with the help of a medical librarian. The following databases were searched for prospective randomized controlled trials (RCTs): PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, and Scopus. The terms “ketamine,” “spine surgery,” and other related terms and word variations were used. The query designed for PubMed can be seen in Appendix A.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were defined and agreed upon by all authors *a priori*. Articles that met the following criteria were eligible for inclusion in the meta-analysis: (1) the article described a human study; (2) ketamine was administered; (3) elective, inpatient spine surgery was performed; (4) the article described a randomized controlled trial; (5) postoperative analgesia was reported; (6) postoperative pain scores were reported (6) postoperative complications were reported; (7) general anesthesia was administered. Articles that met any of the following exclusion criterion were excluded from the meta-analysis: (1) the article described a non-human study; (2) ketamine was only administered for general anesthesia; (3) trauma, outpatient, or non-spine surgery were conducted; (4) the article did not describe a clinical trial; (5) postoperative analgesia was *not* reported; (6) postoperative pain scores were *not* reported; (7) general anesthesia was *not* administered; (8) a treatment

or control arm of the trial comprised 10 patients or fewer; (9) non-English language article. The results were updated as of February 4th, 2015.

Article Screening

Duplicate articles were removed from the results of the systematic search of each database. The remaining titles and abstracts were downloaded and screened independently by two authors (A.P. and S.F.) based on the pre-existing inclusion and exclusion criteria. A third author (M.E.) resolved disagreement. The full texts of the articles were then screened independently by A.P. and S.F. and disputes once again resolved by M.E. Kappa scores were used to quantify inter-rater agreement. All articles remaining after the second round of screening were included in the meta-analysis.

Data Abstraction

Data were abstracted from the included studies by one author (A.P.). The corresponding author of each study was contacted individually for additional raw or grouped data; data requests were granted by the corresponding authors of 2 studies[5–6]. The following study characteristics were recorded: first author, publication year, and number of subjects. Also, the mode, dosage, and timing of ketamine administration were documented. Other recorded data included placebo control (saline) and the primary postoperative analgesic. Outcomes were only analyzed if reported by at least 3 studies. Continuous outcomes included opioid consumption and postoperative pain scores at rest. Dichotomous outcomes included adverse events such as bad dreams, cardiac events, dysphoria, hallucinations, headache, postoperative nausea and vomiting (PONV), pruritus, psychotomimetic effects, respiratory depression, sedation, and urinary retention. In articles that reported more than one treatment arm, treatment arms were combined to create a single pair-wise comparison as described by Higgins *et al*[7].

Data Normalization

With the help of biostatisticians, abstracted data were normalized prior to analysis. Opioid consumption was analyzed after converting all non-morphine primary postoperative analgesics such as fentanyl (100:1 potency[8]) and hydromorphone (5:1 potency[9]) to morphine equivalents. This was necessary for 5 studies[10–14]. Due to differences in the reporting of opioid consumption, estimation of the average cumulative morphine equivalent consumption was necessary for several studies. In 4 studies, we standardized weight-adjusted means and standard deviations by multiplying by average weight and using the product of the variances to produce a crude estimate of the standard deviation[6,10,15–16]. In one study, the cumulative opioid consumption was estimated from infusion rate[15]. In trials that did not report cumulative opioid consumption but described opioids consumed over select time periods (*e.g.* 0–24hrs, 24–48hrs…), the average cumulative analgesic was calculated and the standard deviations were imputed by entering the largest available standard deviations, thereby producing a conservative estimate. A series of sensitivity analyses were conducted to determine the effect of these estimations.

At rest pain scores were reported on a 0–10 scale by 8 studies[6,11,13,15–19], 0–5 scale by 2 studies[20–21], and 0–100 scale by 4 studies[5,10,13–14]. Means and standard deviations of pain scores were normalized to a 0–10 scale prior to comparison.

Normalization was required for the following dichotomous outcomes: unpleasant dreams, cardiac events, dysphoria, hallucinations, PONV, and sedation. PONV was reported as a combined event in 5 studies and separately (experiences of nausea and/or number of emesis) in 3 studies. In the latter case, the incidence of vomiting was recorded preferentially. Cardiac events included arrhythmia, circulatory depression, and/or major changes in heart rate or blood pressure. Several studies (n=3) reported dysphoria while 7 reported unpleasant dreams and 8 reported hallucinations separately. Although sedation was analyzed as a dichotomous outcome, sedation was reported as a continuous outcome in 3 articles. In such cases, the corresponding author was contacted for additional data; supplementary data were obtained for 2 studies. Sedation was recorded for any score of 5 or above (on a 0–5 scale), mention of deep sedation, and/or description of response only with any, repeated, or painful stimuli in accordance with guidelines established by the American Society of Anesthesiologists (ASA)[22].

Statistical Analysis

Microsoft® Excel for Mac Version 15.11.12 and Review Manager 5.3.5 for Mac were used to conduct the analysis[23]. The Cochrane Handbook was used as a reference[7]. For continuous outcomes such as opioid consumption, postoperative pain scores, and length of stay, mean differences (MD) and 95% confidence intervals (CI) were calculated. Odds ratio (OR) and 95% CI were calculated for dichotomous outcomes (adverse events). Chi-squared analysis was used to test for heterogeneity between studies with a significance value set at 0.10 in order to more accurately detect significant heterogeneity[24]. Heterogeneity was further quantified by applying the I^2 test with values exceeding 50% indicating considerable or substantial heterogeneity[7]. The random effects model was used to incorporate between-studies heterogeneity for comparisons with $p_{\text{hetero}}<0.10$ and $I^2>50\%$; otherwise, the fixed effects model was used[7]. Before incorporating supplementary data obtained from corresponding authors, sensitivity analyses were conducted.

RESULTS

Systematic Search and Article Screening

The systematic search yielded 1846 articles from PubMed (n=618), Web of Science (n=413), Scopus (n=208), and the Cochrane Central Register of Controlled Trials (n=607). A total of 696 duplicate publications were removed. The remaining 1150 articles were reviewed by title and abstract such that 1127 were excluded (κ=0.6). The remaining 23 articles were screening for eligibility based on full-text review. Another 9 articles were discarded and a final tally of 14 articles were included in the qualitative and quantitative synthesis (κ=0.5). Figure 1 diagrams the article screening process.

Included Studies

A total of 14 randomized controlled trials comprising 649 patients were included in the meta-analysis. Study characteristics are provided in Table 1.

Morphine Equivalent Consumption

Postoperative morphine equivalent consumption and postoperative pain scores are documented in Table 2. Patients in the ketamine group exhibited significantly less morphine equivalent consumption 4 hours following surgery (MD: −5.69, 95% CI: −10.73 to −0.65, p=0.03). At 8 hours, the ketamine group again was associated with lower opioid consumption (MD: −8.16, 95% CI: −10.54 to −5.78, p<0.001). Patients in the ketamine group also consumed fewer cumulative morphine equivalents at 12 hours after surgery as well (MD: −7.06, 95% CI: −12.99 to −1.13, p=0.02). The difference in cumulative opioid consumption was most pronounced at 24 hours following surgery, with patients that were administered ketamine consuming significantly fewer morphine equivalents (MD: −14.38, 95% CI: −18.13 to −10.62, p<0.001). However, the difference in opioid consumption was no longer significant at 36 hours (MD: −8.64, 95% CI: −18.62 to 1.33, p=0.09). At 48 hours, patients in the ketamine group had consumed more morphine equivalents compared to control, though this difference was not statistically significant (MD: 2.39, 95% CI: −10.42 to 15.21, p=0.71). Forest plots for morphine equivalent consumption at 12, 24, and 48 hours are reported in Figures 2, 3, and 4, respectively.

Pain Scores

Immediately following surgery, there was no statistical difference in average pain scores between groups (MD: −0.18, 95% CI: −0.69 to 0.33, p=0.48). At 1 hour, once again there was no significant difference (MD: −1.02, 95% CI: −2.46 to 0.42, p=0.16). However, at 6 hours following surgery, patients in the ketamine group indicated significantly lower pain scores compared to control (MD: −1.18, 95% CI: −1.67 to −0.69, p<0.001). The ketamine group was also associated with lower average pain scores at 12 hours (MD: −1.01, 95% CI: −1.51 to −0.52, p<0.001). At 24 hours, patients in the ketamine group continued to report lower pain scores compared to control (MD: −1.27, 95% CI: −1.70 to −0.84, p<0.001). However, by 36 hours, there was no statistically significant difference between the pain scores of each group (MD: 0.15, 95% CI: −1.15 to 1.44, p=0.83). At 48 hours, the difference in pain scores was again not statistically significant (MD: −0.35, 95% CI: −0.96 to 0.26, p=0.26). By 72 hours, there was nearly no difference in average pain scores between groups (MD: 0.04, 95% CI: −0.36 to 0.43, p=0.85). Forest plots for postoperative pain scores at 12, 24, and 48 hours are reported in Figures 5, 6, and 7, respectively.

Adverse Events

Adverse events are documented in Table 3. Unpleasant dreams were reported in 2 patients administered ketamine compared to none in the control group (OR: 3.19, 95% CI: 0.32 to 31.81, p=0.32). Cardiac events were reported in 1 case in the control group compared to none in the ketamine group (OR: 0.31, 95% CI: 0.01 to 8.28, p=0.49). Dysphoria occurred in 2 patients that received ketamine and in 3 patients in the control group (OR: 0.64, 95% CI: 0. 09 to 4.27, p=0.64). Patients that were given ketamine experienced twice as many

hallucinations (4 events) compared to control (2 events) (OR: 1.58, 95% CI: 0.30 to 8.43, p=0.59). Headache was experienced in 5 patients that received ketamine compared to 3 patients in the control cohort (OR: 1.34, 95% CI: 0.30 to 6.01, p=0.71). Incidence of PONV occurred in 42 and 41 patients in the ketamine group and control group, respectively (OR: 0.80, 95% CI: 0.44 to 1.45, p=0.46). Pruritus was experienced by 14 patients given ketamine and 11 patients in the control group (OR: 2.14, 95% CI: 0.64 to 7.21, p=0.22). Psychotomimetic events occurred in 3 patients administered ketamine but in 0 patients in the control group (OR: 3.95, 95% CI: 0.19 to 81.49, p=0.37). Respiratory depression was found in 2 ketamine patients compared to 4 control patients (OR: 0.42, 95% CI: 0.06 to 2.77, p=0.37). Patients that received ketamine experienced more sedation (5 events) compared to control (3 events) (OR: 1.34, 95% CI: 0.29 to 6.24, p=0.71). Urinary retention was not encountered in the ketamine group but occurred once in the control group (OR: 0.31, 95% CI: 0.01 to 8.28, p=0.49).

DISCUSSION

Ketamine has been discussed in the literature extensively as a supplemental analgesic for perioperative pain control. Although several reviews have reported a statistically significant decrease in opioid analgesic consumption with use of ketamine, whether this holds true for spine surgery is not certain[4,25]. According to the findings of this meta-analysis, addition of supplemental ketamine yielded a significant reduction in postoperative morphine equivalent consumption at 4 hours, 8 hours, 12 hours, and 24 hours postoperatively. However, this statistically significant opioid sparing effect was no longer apparent at 36 hours following surgery. By 48 hours after surgery, patients that had been administered ketamine actually had a greater cumulative opioid consumption compared to their counterparts, though this was not considered statistically significant.

With regards to postoperative pain, patients in the ketamine group reported lower pain scores, on average, throughout the postoperative period (at 0, 1, 6, 12, 24, 36, 48, and 72 hours after surgery). Although the difference in pain scores immediately after surgery (0–1 hour) was not significant, patients in the ketamine reported significantly lower average pain scores at 6, 12, and 24 hours following surgery. This reduction in pain scores mirrors the reduction in cumulative morphine equivalent consumption during the first postoperative day. In addition, any difference in pain scores after 24 hours (36, 48, and 72 hours after surgery) was not significant. As a result, the significant reduction in morphine equivalent consumption by patients in the ketamine group during the first 24 hours following surgery coincided with significantly reduced pain scores during that same period, with the exception of the first postoperative hour. These findings suggest that the analgesia provide by supplemental low-dose ketamine may be confined to the first 24 hours following spine surgery.

Notably, this meta-analysis showed the opiate-sparing effects and postoperative pain reduction due to ketamine demonstrated efficacy exclusively within the first 24 hours postoperatiely. This ‘window effect’ may stem from differences in timing, dose, or mode of ketamine among trials. For example, ketamine was administered solely intraoperatively in several trials; given that the half-life of ketamine is approximately 186 minutes, analgesic

effects may dissipate soon after intraoperative infusion is terminated[26]. Another possible explanation may be dosing: Pestieau *et al* reduced ketamine dosage when transitioning from the intraoperative to postoperative period[16]. Furthermore, in several trials, continuous IV infusions during the intraoperative period were replaced by IV-PCA postoperatively, introducing variables such as patient decision-making and differences in lockout intervals. Finally, opiate-tolerant patients may respond differently to ketamine, most notably at 48 hours and beyond. For example, Subramaniam *et al*. included subjects with pre-operative opiate use, finding low-dose ketamine to be ineffective[11]. Although many trials excluded patients with pre-operative narcotic use, other did not acknowledge pre-operative opiate consumption, leaving it unclear as to whether opiate tolerant patients were included and if so, how many. As a result, if chronic opiate use mitigated ketamine analgesia, the magnitude of this effect is indeterminate with the available data to include.

Delirium has been reported to occur in 5–15% of patients undergoing non-cardiac surgery and ketamine has been noted to cause delirium[27–28]. Although delirium was not explicitly reported by the trials included in this meta-analysis, several adverse events commonly associated with delirium were studied: unpleasant dreams, hallucinations, psychotomimetic events, and dysphoria. None of the aforementioned complications achieved statistical significance. These findings are contrary to previous reports. For example, ketamine as an anesthetic agent has been associated with dysphoria in as many as 10–20% of adult patients after a variety of surgical procedures[29]. However, sub-anesthetic doses of ketamine, such as those that may be used for supplemental analgesia, has been reported to reduce the occurrence of dysphoria. Also, ketamine has previously been associated with a reduction in postoperative nausea and vomiting, though no such difference was detected in this study[4,30]. In terms of cardiac events, headaches, respiratory depression, and urinary retention, there were no significant differences between groups.

Recent trends in spine surgery involve eschewing opiates in favor of non-opiate agents due to suboptimal opiate-related side effects[2]. One such non-opiate agent is ketamine, which has been noted to prevent opiate-induced hyperalgesia, the paradoxical heightened sensitive to pain following opiate exposure[31–32]. Given the short-term reduction in both morphine equivalent consumption and postoperative pain scores without an increase in complication rates, this meta-analysis offers an informed choice with new knowledge supporting either use or non-use of ketamine in the perioperative period based on individual interpretation of the objective results.

Limitations

Despite an exhaustive and systematic search of multiple databases, it is possible that there exist trials of ketamine use that were not included in this study. Furthermore, of the trials that were included, there was often significant heterogeneity in the comparisons. For example, the modes of administration included single bolus (n=9), continuous infusion (n=10), and IV-PCA (n=5). Dosages also differed considerably, weight-adjusted doses were utilized in several trials (n=4), and timing of administration varied from intraoperatively (n=4), postoperatively (n=2) trials, and both intra- and postoperatively (n=8). This study was not designed to evaluate dose-dependency so although supplemental ketamine yielded a

significant reduction in morphine equivalent consumption for the first 24 hours, the optimal dose remains unclear. Furthermore, combining low- and high-dose treatment arms may have produced a moderating effect. Similarly, this meta-analysis was not structured to compare the mode or timing of ketamine administration, but determining the optimal dose and/or the ideal timing of intravenous ketamine may constitute avenues for future prospective studies. Although none of the adverse events obtained statistical significance, it is possible that this study was not adequately powered to detect differences in complication rates as evidence by several instances in which either the ketamine group or control contained no patients that experienced a complication.

Conclusion

This meta-analysis of supplemental ketamine for analgesia in spine surgery found a consistent opioid analgesic sparing effect over the course of 24 hours following surgery. With the exception of the first hour, this reduction in analgesic consumption coincided with significant reduced pain scores. Notably, significant reductions in both morphine equivalent consumption and pain scores did not persist beyond the first 24 hours, suggesting that the analgesic effect of supplemental ketamine may be limited to this timeframe. Furthermore, there was significant heterogeneity associated with the trials that were included in this study. Although this study indicates that low-dose supplemental ketamine may be useful for short-term analgesia following spine surgery, this meta-analysis was not designed to evaluate dose, timing, or mode of ketamine administration, all of which constitute avenues for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

1. Supplemental ketamine reduced cumulative morphine equivalent consumption at 4, 8, 12, and 24 hours after spine surgery.
2. Supplemental ketamine reduced postoperative pain scores at 6, 12, and 24 hours after spine surgery.
3. Supplemental ketamine did not predispose spine surgery patients to an increased odds of experiencing unpleasant dreams, cardiac events, dysphoria, hallucinations, postoperative nausea or vomiting, pruritus, psychotomimetic events, respiratory depression, sedation, or urinary retention.

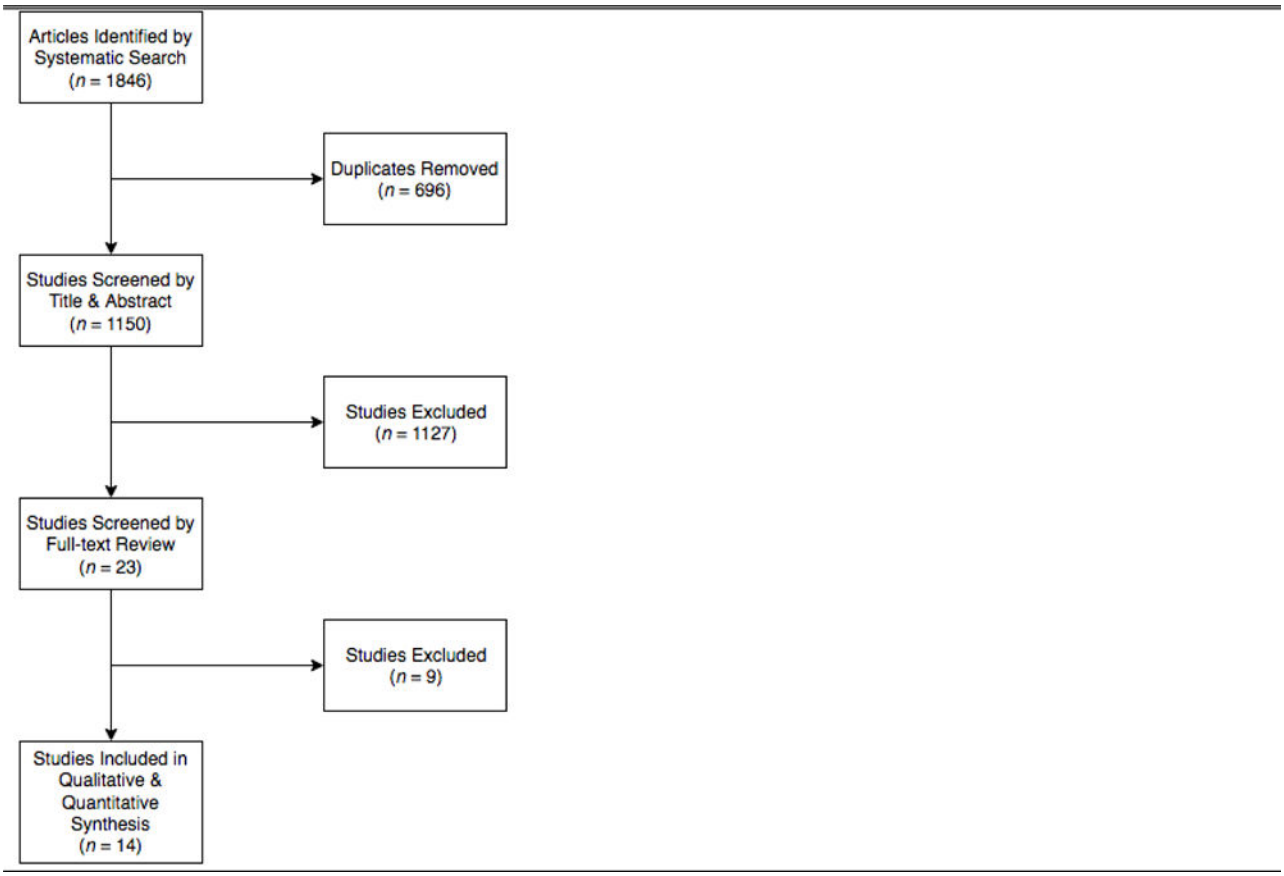

Figure 1.
Flow Diagram

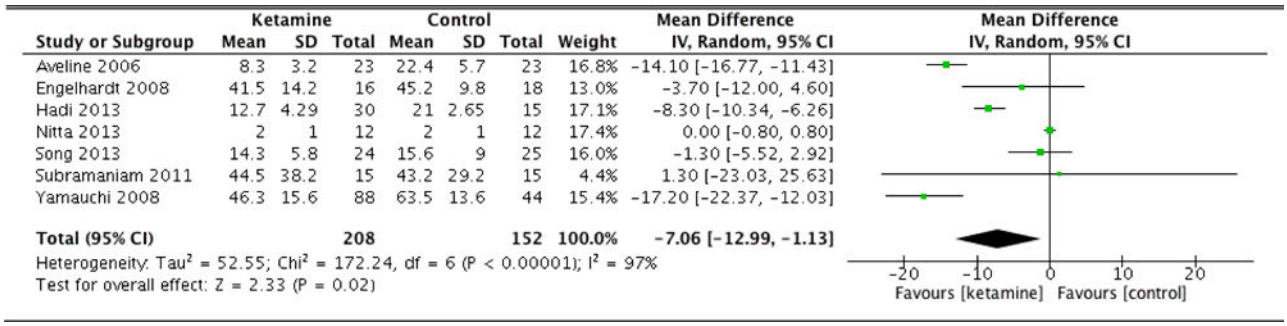

Figure 2.
Morphine equivalent consumption at 12 hours

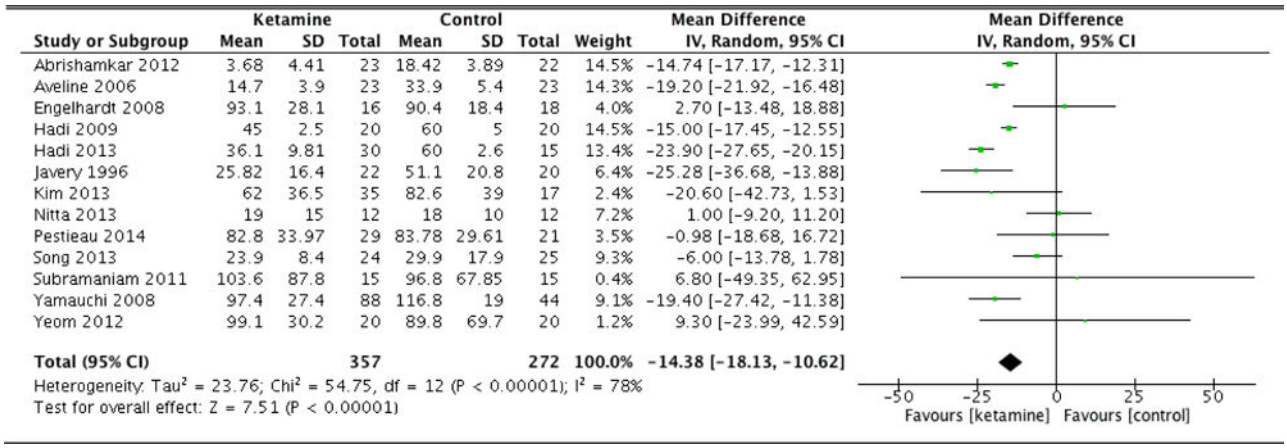

Figure 3.
Morphine equivalent consumption at 24 hours

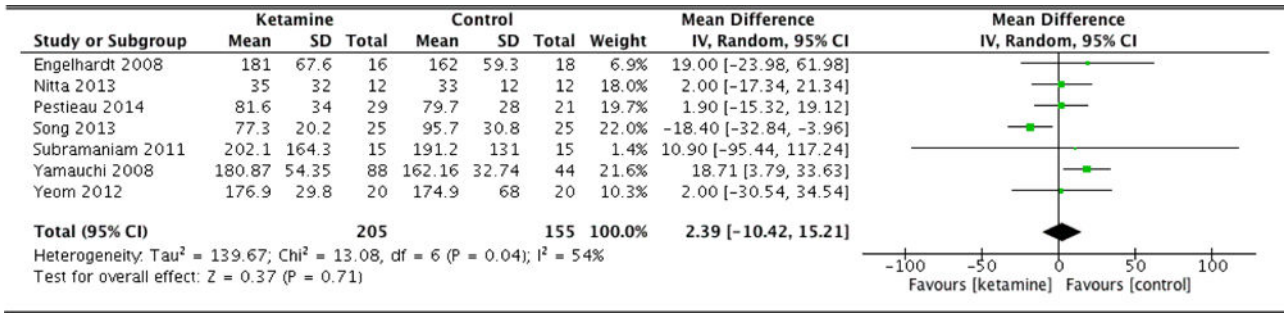

Figure 4.
Morphine equivalent consumption at 48 hours

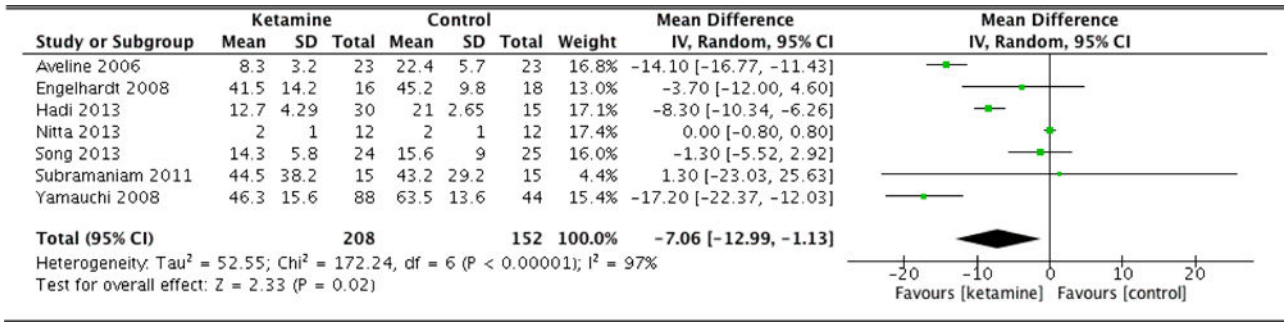

Figure 5.
Postoperative pain scores at 12 hours

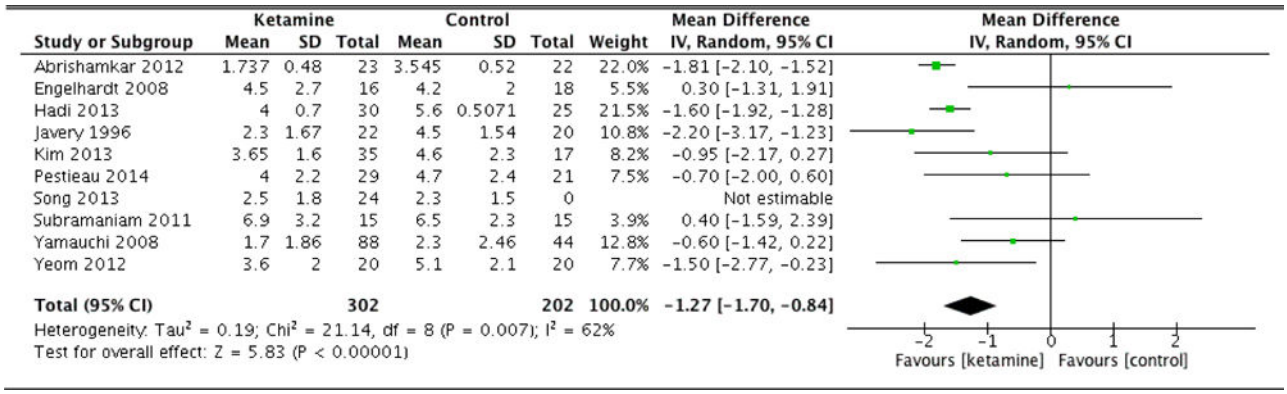

Figure 6.
Postoperative pain scores at 24 hours

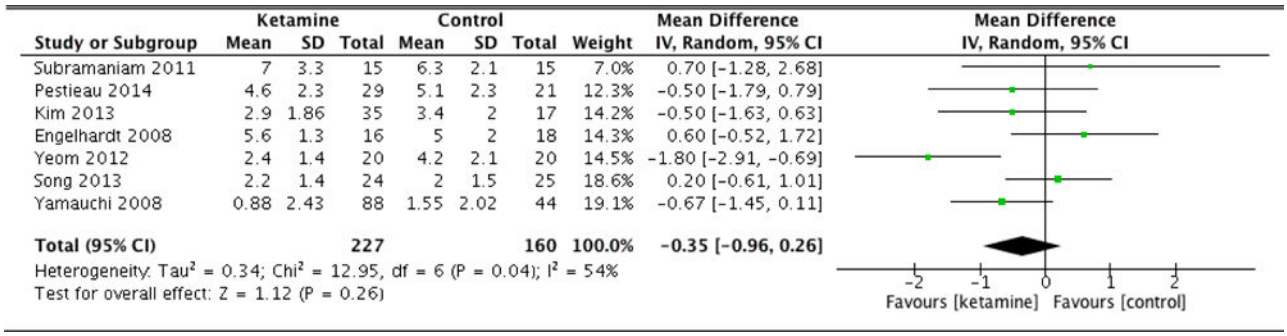

Figure 7.
Postoperative pain scores at 48 hours

Table 1

Study Characteristics

First author	Publication Year	Number of Subjects		Ketamine			Control Saline	Primary postoperative analgesic	
		Ketamine	Control	Mode	Dosage	Timing		Analgesic	Mode
Javery	1996	22	20	IV-PCA	1 mg ml^{-1}	Postoperative		Morphine	IV-PCA
Aveline	2006	23	23	Bolus	0.15 mg kg^{-1}	Intraoperative		Morphine	IV-PCA
Engelhardt	2008	16	18	Bolus Continuous infusion	0.5 mg/kg 4 μg kg^{-1} min^{-1}	Intraoperative Intraoperative	Saline	Morphine	IV-PCA
Yamauchi	2008	88	44	Bolus Continuous infusion	1 mg kg^{-1} 42–83 μg kg^{-1} min^{-1}	Intraoperative Intraoperative	Saline	Fentanyl	IV-PCA
Hadi	2009	20	20	Continuous infusion	4 μg kg^{-1} min^{-1}	Intraoperative		Morphine	IV-PCA
Subramaniam	2011	15	15	Bolus Continuous infusion	0.15 mg kg^{-1} 2 μg kg^{-1} min^{-1}	Intraoperative Intraoperative Postoperative	Saline	Hydromorphone	IV-PCA
Abrishamkar	2012	22	23	Continuous infusion	0.5 mg kg^{-1} hr^{-1}	Postoperative		Morphine	IV
Pacreu	2012	10	10	Bolus Continuous infusion IV-PCA	0.5 mg kg^{-1} 2.5 μg kg^{-1} min^{-1} 0.5 mg	Intraoperative Intraoperative Postoperative	Saline	Methadone	IV-PCA
Yeom	2012	20	20	Bolus IV-PCA	0.2 mg/kg 30 μg ml^{-1} kg^{-1}	Intraoperative Postoperative	Saline	Fentanyl	IV-PCA
Hadi	2013	30	15	Continuous infusion	1 μg kg^{-1} min^{-1}	Intraoperative Postoperative	Saline	Morphine	IV
Kim	2013	35	17	Bolus Continuous infusion	0.5 mg kg 1–2 μg kg^{-1} min^{-1}	Intraoperative Postoperative	Saline	Fentanyl	IV-PCA
Nitta	2013	12	12	Bolus IV-PCA	10 mg kg^{-1} 2 mg kg^{-1} hr^{-1}	Intraoperative Postoperative		Morphine	IV-PCA
Song	2013	25	24	Continuous infusion IV-PCA	0.3 mg kg^{-1} 3 mg kg^{-1}	Intraoperative Postoperative	Saline	Fentanyl	IV-PCA
Pestieau	2014	29	21	Bolus Continuous infusion Continuous infusion	0.5 mg kg^{-1} 0.2 mg kg^{-1} hr^{-1} 0.1 mg kg^{-1} hr^{-1}	Intraoperative Intraoperative Postoperative	Saline	Morphine	IV-PCA

Spine (Phila Pa 1976). Author manuscript; available in PMC 2019 March 01.

Table 2

Postoperative morphine equivalent consumption and postoperative pain score

Outcome	# of studies	Sample size: ketamine (control)	Analysis Model	MD (95% CI)	*p* Hetero	*p* Effect
Morphine equivalents (4hrs)	3	54 (56)	Random Effects	−5.69 (−10.73 to −0.65)	0.02	0.03
Morphine equivalents (8hrs)	3	54 (56)	Fixed Effects	−8.16 (−10.54 to −5.78)	0.34	<0.001
Morphine equivalents (12hrs)	7	208 (152)	Random Effects	−7.06 (−12.99 to −1.13)	<0.001	0.02
Morphine equivalents (24hrs)	13	357 (272)	Random Effects	−14.38 (−18.13 to −10.62)	<0.001	<0.001
Morphine equivalents (36hrs)	3	51 (52)	Fixed Effects	−8.64 (−18.62 to 1.33)	0.18	0.09
Morphine equivalents (48hrs)	7	205 (155)	Random Effects	2.39 (−10.42 to 15.21)	0.04	0.71
Pain scores (0h)	4	78 (80)	Fixed Effects	−0.18 (−0.69 to 0.33)	0.60	0.48
Pain scores (1hrs)	5	158 (96)	Random Effects	−1.02 (−2.46 to 0.42)	<0.001	0.16
Pain scores (6hrs)	5	200 (123)	Random Effects	−1.18 (−1.67 to −0.69)	0.03	<0.001
Pain scores (12hrs)	6	196 (139)	Random Effects	−1.01 (−1.51 to −0.52)	0.03	<0.001
Pain scores (24hrs)	10	302 (202)	Random Effects	−1.27 (−1.70 to −0.84)	0.007	<0.001
Pain scores (36hrs)	4	143 (102)	Random Effects	0.15 (−1.15 to 1.44)	0.002	0.83
Pain scores (48hrs)	7	227 (160)	Random Effects	−0.35 (−0.96 to 0.26)	0.04	0.26
Pain scores (72hrs)	3	133 (83)	Fixed Effects	0.04 (−0.36 to 0.43)	0.05	0.85

MD: mean difference; CI: confidence interval; p: p-value

Table 3

Adverse events

Outcome	# of studies	Events [Ketamine total]	Events [Control total]	Analysis Model	OR (95% CI)	*p* Hetero	*p* Effect
Unpleasant dreams	7	2 [235]	0 [168]	Fixed Effects	3.19 (0.32 to 31.81)	0.99	0.32
Cardiac events	4	0 [144]	1 [92]	Random Effects	0.31 (0.01 to 8.28)	n/a	0.49
Dysphoria	3	2 [66]	3 [65]	Fixed Effects	0.64 (0.09 to 4.27)	0.22	0.64
Hallucination	9	4 [215]	2 [176]	Fixed Effects	1.58 (0.30 to 8.43)	0.43	0.59
Headache	3	6 [60]	3 [42]	Fixed Effects	1.34 (0.30 to 6.01)	0.58	0.71
PONV	7	42 [161]	41 [130]	Fixed Effects	0.80 (0.44 to 1.45)	0.12	0.46
Pruritus	4	14 [129]	11 [87]	Fixed Effects	2.14 (0.64 to 7.21)	0.84	0.22
Psychotomimetic effects	3	3 [64]	0 [50]	Random Effects	3.95 (0.19 to 81.49)	n/a	0.37
Respiratory depression	8	2 [219]	4 [165]	Random Effects	0.42 (0.06 to 2.77)	n/a	0.37
Sedation	4	5 [89]	3 [73]	Fixed Effects	1.34 (0.29 to 6.24)	0.55	0.71
Urinary retention	3	0 [126]	1 [82]	Random Effects	0.31 (0.01 to 8.28)	n/a	0.49

OR: odds ratio; CI: confidence interval; p: p-value; PONV: postoperative nausea and vomiting