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Perioperative intravenous ketamine for acute postoperative pain in adults (Review)

Brinck ECV, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 6
OBJECTIVES 7
METHODS 7
RESULTS 11
Figure 1. 12
Figure 2. 14
Figure 3. 15
DISCUSSION 28
AUTHORS' CONCLUSIONS 31
ACKNOWLEDGEMENTS 31
REFERENCES 33
CHARACTERISTICS OF STUDIES 48
DATA AND ANALYSES 180
Analysis 1.1. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 1: Opioid consumption at 24 hours 182
Analysis 1.2. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 2: Opioid consumption at 48 hours 183
Analysis 1.3. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 3: Pain intensity at rest at 24 hours 184
Analysis 1.4. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 4: Pain intensity during movement at 24 hours 186
Analysis 1.5. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 5: Pain intensity at rest at 48 hours 187
Analysis 1.6. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 6: Pain intensity during movement at 48 hours 188
Analysis 1.7. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 7: Time to first request for analgesia/trigger of PCA 189
Analysis 1.8. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 8: CNS adverse events - all studies 190
Analysis 1.9. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 9: Hyperalgesia 192
Analysis 1.10. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 10: CNS adverse events - studies with events 193
Analysis 1.11. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 11: Postoperative nausea and vomiting - all studies 195
Analysis 2.1. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 1: Opioid consumption at 24 hours 198
Analysis 2.2. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 2: Opioid consumption at 48 hours 199
Analysis 2.3. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 3: Pain intensity at 24 hours 200
Analysis 2.4. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 4: Pain intensity at 48 hours 201
Analysis 2.5. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 5: Time to first request for analgesia/first trigger of PCA 201
Analysis 3.1. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 1: Opioid consumption at 24 hours 203
Analysis 3.2. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 2: Opioid consumption at 48 hours 204

Analysis 3.3. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 3: Pain intensity at rest at 24 hours 205
Analysis 3.4. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 4: Pain intensity during movement at 24 hours 206
Analysis 3.5. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 5: Pain intensity at rest at 48 hours 206
Analysis 3.6. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 6: Pain intensity during movement at 48 hours 207
Analysis 4.1. Comparison 4: CNS adverse events in studies with benzodiazepine premedication, Outcome 1: CNS adverse events 208
Analysis 5.1. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 1: Opioid consumption at 24 hours 210
Analysis 5.2. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 2: Opioid consumption at 48 hours 210
Analysis 5.3. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 3: Pain intensity at rest at 24 hours 210
Analysis 5.4. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 4: Pain intensity during movement at 24 hours 211
Analysis 5.5. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 5: Pain intensity at rest at 48 hours 211
Analysis 5.6. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 6: Pain intensity during movement at 48 hours 211
Analysis 6.1. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 1: Opioid consumption at 24 hours 212
Analysis 6.2. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 2: Opioid consumption at 48 hours 213
Analysis 6.3. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 3: Pain intensity at rest at 24 hours 213
Analysis 6.4. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 4: Pain intensity during movement at 24 hours 213
Analysis 6.5. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 5: Pain intensity at rest at 48 hours 214
Analysis 6.6. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 6: Pain intensity during movement at 48 hours 214
Analysis 7.1. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 1: Opioid consumption at 24 hours 215
Analysis 7.2. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 2: Opioid consumption at 48 hours 215
Analysis 7.3. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 3: Pain intensity at rest at 24 hours 216
Analysis 7.4. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 4: Pain intensity during movement at 24 hours 216
Analysis 7.5. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 5: Pain intensity at rest at 48 hours 217
Analysis 7.6. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 6: Pain intensity during movement at 48 hours 217
Analysis 8.1. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 1: Opioid consumption at 24 hours 218
Analysis 8.2. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 2: Opioid consumption at 48 hours 218
Analysis 8.3. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 3: Pain intensity at rest at 24 hours 218
Analysis 9.1. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 1: Opioid consumption at 24 hours 219
Analysis 9.2. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 2: Opioid consumption at 48 hours 219
Analysis 9.3. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 3: Pain intensity at rest at 24 hours 220
APPENDICES 220
WHAT'S NEW 226

HISTORY 226
CONTRIBUTIONS OF AUTHORS 227
DECLARATIONS OF INTEREST 227
SOURCES OF SUPPORT 227
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 227
NOTES 228
INDEX TERMS 228

[Intervention Review]

Perioperative intravenous ketamine for acute postoperative pain in adults

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ABSTRACT

Background

Inadequate pain management after surgery increases the risk of postoperative complications and may predispose for chronic postsurgical pain. Perioperative ketamine may enhance conventional analgesics in the acute postoperative setting.

Objectives

To evaluate the efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia.

Search methods

We searched CENTRAL, MEDLINE and Embase to July 2018 and three trials registers (metaRegister of controlled trials, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)) together with reference checking, citation searching and contact with study authors to identify additional studies.

Selection criteria

We sought randomised, double-blind, controlled trials of adults undergoing surgery under general anaesthesia and being treated with perioperative intravenous ketamine. Studies compared ketamine with placebo, or compared ketamine plus a basic analgesic, such as morphine or non-steroidal anti-inflammatory drug (NSAID), with a basic analgesic alone.

Data collection and analysis

Two review authors searched for studies, extracted efficacy and adverse event data, examined issues of study quality and potential bias, and performed analyses. Primary outcomes were opioid consumption and pain intensity at rest and during movement at 24 and 48 hours postoperatively. Secondary outcomes were time to first analgesic request, assessment of postoperative hyperalgesia, central nervous system (CNS) adverse effects, and postoperative nausea and vomiting. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

We included 130 studies with 8341 participants. Ketamine was given to 4588 participants and 3753 participants served as controls. Types of surgery included ear, nose or throat surgery, wisdom tooth extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, knee joint replacement surgery, anterior cruciate ligament repair, knee arthroscopy, mastectomy, haemorrhoidectomy, abdominal surgery, radical prostatectomy, thyroid surgery, elective caesarean section, and laparoscopic surgery. Racemic ketamine bolus doses were predominantly 0.25 mg to 1 mg, and infusions 2 to 5 µg/kg/minute; 10 studies used only S-ketamine and one only R-ketamine. Risk of bias was generally low or uncertain, except for study size; most had fewer than 50 participants per treatment arm, resulting in high heterogeneity, as expected, for most analyses. We did not stratify the main analysis by type of surgery or any other factor, such as dose or timing of ketamine administration, and used a non-stratified analysis.

Perioperative intravenous ketamine reduced postoperative opioid consumption over 24 hours by 8 mg morphine equivalents (95% CI 6 to 9; 19% from 42 mg consumed by participants given placebo, moderate-quality evidence; 65 studies, 4004 participants). Over 48 hours, opioid consumption was 13 mg lower (95% CI 10 to 15; 19% from 67 mg with placebo, moderate-quality evidence; 37 studies, 2449 participants).

Perioperative intravenous ketamine reduced pain at rest at 24 hours by 5/100 mm on a visual analogue scale (95% CI 4 to 7; 19% lower from 26/100 mm with placebo, high-quality evidence; 82 studies, 5004 participants), and at 48 hours by 5/100 mm (95% CI 3 to 7; 22% lower from 23/100 mm, high-quality evidence; 49 studies, 2962 participants). Pain during movement was reduced at 24 hours (6/100 mm, 14% lower from 42/100 mm, moderate-quality evidence; 29 studies, 1806 participants), and 48 hours (6/100 mm, 16% lower from 37 mm, low-quality evidence; 23 studies, 1353 participants).

Results for primary outcomes were consistent when analysed by pain at rest or on movement, operation type, and timing of administration, or sensitivity to study size and pain intensity. No analysis by dose was possible. There was no difference when nitrous oxide was used. We downgraded the quality of the evidence once if numbers of participants were large but small-study effects were present, or twice if numbers were small and small-study effects likely but testing not possible.

Ketamine increased the time for the first postoperative analgesic request by 54 minutes (95% CI 37 to 71 minutes), from a mean of 39 minutes with placebo (moderate-quality evidence; 31 studies, 1678 participants). Ketamine reduced the area of postoperative hyperalgesia by 7 cm^2 (95% CI −11.9 to −2.2), compared with placebo (very low-quality evidence; 7 studies 333 participants). We downgraded the quality of evidence because of small-study effects or because the number of participants was below 400.

CNS adverse events occurred in 52 studies, while 53 studies reported of absence of CNS adverse events. Overall, 187/3614 (5%) participants receiving ketamine and 122/2924 (4%) receiving control treatment experienced an adverse event (RR 1.2, 95% CI 0.95 to 1.4; high-quality evidence; 105 studies, 6538 participants). Ketamine reduced postoperative nausea and vomiting from 27% with placebo to 23% with ketamine (RR 0.88, 95% CI 0.81 to 0.96; the number needed to treat to prevent one episode of postoperative nausea and vomiting with perioperative intravenous ketamine administration was 24 (95% CI 16 to 54; high-quality evidence; 95 studies, 5965 participants).

Authors' conclusions

Perioperative intravenous ketamine probably reduces postoperative analgesic consumption and pain intensity. Results were consistent in different operation types or timing of ketamine administration, with larger and smaller studies, and by higher and lower pain intensity. CNS adverse events were little different with ketamine or control. Perioperative intravenous ketamine probably reduces postoperative nausea and vomiting by a small extent, of arguable clinical relevance.

PLAIN LANGUAGE SUMMARY

Ketamine venous injection for acute pain after operation in adults

Bottom line

Ketamine injected into a vein at the time of operation reduces pain, nausea and vomiting, and use of opioid (morphine-like) painkillers after operation.

Background

Poor pain management after an operation increases the risk of complications, decreases quality of life, and increases the risk for chronic pain. Painkillers such as paracetamol and non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac), alone may be insufficient. Opioids (strong painkillers), often cause side effects. Studies suggested that ketamine used by injection during an operation helps to relieve pain after the operation.

Study characteristics

In July 2018 we searched for randomised clinical trials where ketamine was injected before, during, or after operation in adults having an operation under general anaesthesia. Important outcomes were opioid use and pain at 24 and 48 hours after the operation, time to first request for a painkiller, and ketamine-related side effects. We found 130 eligible studies with 8341 participants.

Key findings

Compared to people given control treatment, those given intravenous ketamine used less opioid painkiller (by about 1 part in 10), and had less pain (by about 2 parts in 10; moderate- or high-quality evidence). Ketamine may be more effective in operations that are likely to cause more intense pain. People given ketamine requested painkillers 54 minutes later than those who did not receive ketamine (moderate-quality evidence). Ketamine reduced the risk of postoperative nausea and vomiting by a small amount (high-quality evidence). Ketamine produced no increased risk of central nervous system side effects (hallucination, nightmares or double vision) (high-quality evidence).

Future research should assess ketamine's effect after operations that are accompanied by intense pain such as thoracotomy, back surgery, or amputations. Additionally, assessing ketamine's effects among particular patient groups, for example, the elderly or individuals with a history of substance abuse would be of interest.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results.

We found the quality of evidence for most outcomes to be moderate. Many of the studies were small, which was the main reason for downgrading the evidence from high to moderate. We tested the results by operation type, timing of ketamine injection, and by looking at larger studies, and those with more pain were consistent, and provided confidence in the results. There was sufficient evidence to allow conclusions about ketamine's effect on pain, painkiller consumption and side effects after operation.

Summary of findings 1. Perioperative intravenous ketamine compared to placebo for acute postoperative pain in adults

Perioperative intravenous ketamine compared to placebo for acute postoperative pain: non-stratified analysis

Patient or population: adults undergoing any type of surgery

Settings: immediate postoperative period

Intervention: intravenous ketamine given before, during, or after surgery

Comparison: intravenous placebo

Outcomes	Details	Number of participants (studies)	Absolute values and effect of ketamine		Quality of the evidence (GRADE)
			Measured values with placebo	Difference with perioperative intravenous ketamine (95% CI)	
Opioid consumption (mg morphine equivalents)	24 hours	4004 (65 RCTs)	Median 31 mg (mean 42 mg)	MD 7.6 mg lower (8.9 lower to 6.4 lower)	Moderate[1]
	48 hours	2449 (37 RCTs)	Median 59 mg (mean 67 mg)	MD 12.6 mg lower (15 lower to 10 lower)	Moderate[1]
Pain intensity (0-100 mm VAS. [7]	At rest 24 hours	5004 (82 RCTs)	Median 25 mm (mean 26 mm)	MD 5 mm (VAS) lower (6.6 lower to 3.6 lower)	High[2]
	On movement 24 hours	1806 (29 RCTs)	Median 43 mm (mean 42 mm)	MD 6 mm (VAS) lower (11 lower to 0.5 lower)	Moderate[1]
	At rest 48 hours	2962 (49 RCTs)	Median 21 mm (mean 23 mm)	MD 5 mm (VAS) lower (6.7 lower to 3.4 lower)	High[2]
	On movement 48 hours	1353 (23 RCTs)	Median 37 mm (mean 37 mm)	MD 6 mm (VAS) lower (10 lower to 1.3 lower)	Low[3]

Time to first request for analgesia/trigger of PCA (minutes)	All data (plus analysis omitting 1 highly aberrant study reporting time of over 1000 minutes)	1678 (31 RCTs)	Median 18 minutes (mean 39 minutes)	MD 54 minutes longer (37 to 71 longer) (MD 22 minutes longer omitting aberrant study (15 to 29 longer))	Moderate[4]
Hyperalgesia (cm^2)	As described, any time point	333 (7 RCTs)	Mean 15 cm^2	MD 7 cm^2 less (12 to 2 less)	Very low[5]
CNS adverse events	All events (major and minor), as described, any time point	6538 (105 RCTs)	52 per 1000	42 per 1000 RR 1.2 (0.95 to 1.4)	High[6]
Postoperative nausea and vomiting	All studies reporting outcomes, as described, any time point	5965 (95 RCTs)	271 per 1000	230 per 1000 RR 0.88 (0.81 to 0.96 Need to treat 24 people to prevent one episode of PONV (16 to 54)	High[6]

CI: confidence interval; **CNS**: central nervous system; **MD**: mean difference; **PCA**: patient controlled analgesia; **PONV:** postoperative nausea and vomiting; **RCT**: randomised controlled trial; **RR**: risk ratio; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once for small study effect.
[2] Not downgraded for small study effect because no reduction in effect with larger studies.
[3] Downgraded once for small study effect, and once because fewer than 1500 participants.
[4] Downgraded once because all studies small, more than 1500 participants but not possible to test for small-study effects.
[5] Downgraded three times because fewer than 400 participants.
[6] Not downgraded: consistent across large body of data.
[7] Lower VAS means less pain.

BACKGROUND

Description of the condition

Inadequate pain management after surgery increases the risk of postoperative complications and it is one of the major risk factors associated with chronic postsurgical pain (Prabhakar 2014; Kehlet 2006). Chronic postsurgical pain is defined as pain that persists for longer than three months (VanDenKerkhof 2013). It adversely affects quality of life and delays rehabilitation and return to usual activities.

Pre-emptive analgesia aims to reduce the risk of acute pain becoming chronic (Katz 2009), but conventional analgesics, such as paracetamol alone, may be insufficient in the acute postoperative period. Adverse events may also limit analgesic use, as is the case with non-steroidal anti-inflammatory drugs (NSAIDs). Neuraxial blocks are not applicable to all patients, as they may mask complications after certain types of surgery (such as spinal surgery), or anticoagulation may limit their use.

Opioids are the most effective drugs for the treatment of acute postoperative pain. These are also widely used for alleviating chronic pain, both malignant and non-malignant, although the use of opioids for chronic non-cancer has recently come to be viewed critically. Several adverse events may accompany the prolonged use of opioids, as well as the development of opioid tolerance and dependency (Macintyre 2010). In addition, the findings of several recent trials have associated opioid use with opioid-induced hyperalgesia, which is characterised by an activation of pronociception. This appears clinically as a paradoxical increase in pain as a result of opioid administration, assuming that there are no other underlying factors (disease progression or a surgical complication). Opioid-induced hyperalgesia results in decreased opioid analgesic efficacy and is distinguishable from opioid tolerance, a condition in which escalating opioid doses may restore analgesic effect.

The development of opioid-induced hyperalgesia is thought to result from neuroplastic changes in the peripheral and central nervous system (CNS), involving both cellular and neural mechanisms (Lee 2011). Firstly, the perturbated action of glutamatergic N-methyl-D-aspartate (NMDA) receptors plays a central role in the development of opioid-induced hyperalgesia. Secondly, continuous opioid administration leads to increased levels of spinal dynorphins, which results in excessive synthesis and release of excitatory neuropeptides, shifting the balance between antinociceptive and pronociceptive systems towards the latter. Thirdly, the descending pathway processing spinal nociceptive impulses reacts to the prolonged opioid administration in a way that results in altered expression and release of different neuropeptides, thus favouring the pronociceptive system (Angst 2006; Mao 2002; Silverman 2009).

The clinical risk factors associated with opioid-induced hyperalgesia are opioid dose and duration of treatment. Genetic factors may also be relevant (Colvin 2010). Susceptibility to opioid-induced hyperalgesia may differ between individual opioid medications (Mao 2002), and can restrict opioid use in pain therapy. Methods to modulate opioid-induced hyperalgesia include the addition of adjuvant therapy that has NMDA-receptor antagonist activity, such as ketamine (Lee 2011; Low 2012).

Description of the intervention

Ketamine is a phencyclidine derivative, first synthesised in 1962. It is a racemic mixture of two optical isomers: R(-) and S(+)–enantiomers. Hepatic cytochrome P450 enzymes metabolise ketamine to norketamine, an active metabolite (Mion 2013; Sigtermans 2009). S-ketamine is approved for clinical use in countries such as Finland and Germany. Its pharmacodynamics are complex. In addition to the competitive antagonism of glutamatergic NMDA receptors, ketamine also inhibits HCN1 ion channels in the forebrain, contributing to its hypnotic action (Benarroch 2013; Chen 2009; Zhou 2013).

Previous reviews have suggested that ketamine is an effective adjuvant drug for the treatment of acute postoperative pain, but it is associated with significant adverse events (Bell 2006; Elia 2005; Laskowski 2011; Schmid 1999; Subramaniam 2004). Both its analgesic effects and adverse events are dose-related and the optimal dose or route of administration are still unknown. Ketamine can be administered either intravenously during general anaesthesia or intravenously via patient-controlled analgesia (PCA) after surgery.

Ketamine causes a dissociative anaesthesia in which the eyes remain open while laryngeal, corneal and pupillary reflexes are conserved. Sensory input reaches the cortical sensory areas but is not perceived, due to suppression of association areas (Aroni 2009). Ketamine does not suppress either respiratory or myocardial function, or haemodynamics, therefore it is a useful anaesthetic agent for critically ill patients, battlefield injuries, or for procedural sedation and analgesia (Eikermann 2012). Its adverse effects are dose-dependent and include hypersalivation, nausea and vomiting; its psychotomimetic effects include vivid dreams, blurred vision, hallucinations, nightmares and delirium. These effects are more common in adult patients and in women (Aroni 2009). S-ketamine is purported to have fewer adverse effects and a shorter sedation time than racemic ketamine (Geisslinger 1993; Marland 2013). For analgesic purposes, subanaesthetic doses (a dose that is below that required to produce anaesthesia), of ketamine are used. This 'low-dose' is defined as a bolus dose of 1 mg/kg intravenous, and for continuous intravenous administration, a dose under 1.2 mg/kg/hour (Peltoniemi 2016). The analgesic potency of S-ketamine is approximately twice that of racemic ketamine (Arendt-Nielsen 1996).

Benzodiazepine premedication reduces the psychotomimetic adverse reactions of both enantiomers. Ketamine combined with the common anaesthetic agent nitrous oxide, an NMDA-receptor antagonist, has exhibited neurotoxic effects in animal studies (Begon 2001; Bulutcu 2002; Jevtović-Todorović 1998). Clinically, this neurotoxic effect might present as psychotomimetic reactions. In animal studies, neurotoxic effects have been prevented by the co-administration of γ-aminobutyric acid (GABA)-ergic agents, for example benzodiazepines (Beals 2003; Jevtovic-Todorovic 2000). It could also be hypothesised that concurrent administration of nitrous oxide with ketamine could abolish the analgesic effects of ketamine as nitrous oxide acts as a weak antagonist to NMDA-receptors.

How the intervention might work

Numerous clinical trials have examined the analgesic properties of ketamine. It has been useful in the treatment of neuropathic pain

(Fisher 2000), and as an adjuvant to opioids in the treatment of refractory pain in people with cancer (Bredlaw 2013). Its analgesic effect is probably mediated via inhibition of NMDA receptors in nociceptive neurons and activation of descending inhibitory monoaminergic pain pathways (Hirota 2011). NMDA receptors play an active role in the processing of nociception in the dorsal horn ganglia of the spinal cord and also play a role in chronic pain states (Ruschweyeh 2011; Sandkühler 2012). Low doses of ketamine alleviate pain because they reduce NMDA receptor-mediated secondary hyperalgesia and the wind-up phenomenon, as well as opioid-induced hyperalgesia via an interaction with opioid receptors (Hirota 2011). Wind-up is a phenomenon whereby responses of dorsal horn neurons increase during repetitive, constant-intensity, C-fibre stimuli (i.e. increased duration and magnitude of the cell responses). Blockade of NMDA receptors has been shown in animal studies to prevent the development of increased pain sensitivity and opioid tolerance (Bell 2006; Mao 2002; Price 2000). Additionally, inhibition of microglial BK channels may contribute to the analgesic effects of ketamine (Hayashi 2011).

Ketamine has been used as an effective adjuvant for analgesia postoperatively, since it reduces pain and opioid requirements (Elia 2005; Subramaniam 2004), and is used as an adjuvant to opioids for cancer pain, though with inadequate evidence (Bell 2017). Bell and colleagues found that ketamine also reduces postoperative nausea and vomiting (Bell 2006). It is of particular benefit for painful procedures including thoracic, upper abdominal and major orthopaedic surgeries (Laskowski 2011). Ketamine may, in addition to its opioid-sparing effect, reduce the development of chronic postoperative pain via inhibition of NMDA receptors and reduction of wind-up and central sensitisation. The optimal dose and route of administration for this indication are as yet unclear.

Why it is important to do this review

Numerous clinical trials and previous reviews have suggested that ketamine is an effective adjuvant drug for acute postoperative pain treatment, but that it has significant adverse effects. Ketamine is widely used in the perioperative setting, with intravenous administration the most common route. Both analgesic and adverse effects are dose-dependent and the optimal dose is still unknown.

A previous Cochrane Review on this topic included trials using different routes of administration (Bell 2006). This review focused on the efficacy and tolerability of ketamine for acute postoperative pain. Earlier reviews on this topic have also included studies where ketamine has been administered intramuscularly, epidurally, subcutaneously and intravenously (Elia 2005; Schmid 1999; Subramaniam 2011). A large number of trials have since been published and it is important to review the current literature using updated Cochrane methodology. This current review is expected to provide important information regarding the optimal dosing of ketamine in the perioperative setting, and to establish a current evidence base for its efficacy and tolerability in the treatment of acute postoperative pain.

OBJECTIVES

To evaluate the efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, prospective, double-blind studies in which:

- participants received ketamine alone or placebo alone as a study drug;
- ketamine was administered in addition to a basic analgesic such as opioid or NSAID in one study group, and compared with a group receiving the same basic analgesic (but without ketamine) in another group;
- pain intensity, use of opioids, or time to first opioid request were reported outcomes;
- the minimum size was 10 participants per arm who completed the study (Moore 1998; Moore 2008).

We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (e.g. meeting reports).

Types of participants

We included adults aged 18 years and above undergoing a surgical procedure under general anaesthesia.

Types of interventions

We included people treated intravenously with ketamine (racemic ketamine or S-ketamine), during general anaesthesia as a bolus dose or as a continuous infusion or, if administered in the postoperative period, via a patient-controlled analgesia device (PCA) or as a continuous intravenous infusion.

Types of outcome measures

Primary outcomes

- Our primary outcome for studies using PCA or opioid as rescue medication was total consumption of opioids in milligrams of morphine equivalents for up to 48 hours after surgery (opioids being the exclusive analgesics used in the included studies).
- Our primary outcome was pain intensity assessed by means of subjective pain scales in studies not assessing or using PCA and in the absence of opioid rescue medication.

We assessed our primary outcomes in a non-stratified study population and by surgery type.

Secondary outcomes

We extracted, assessed, and analysed the following secondary outcomes.

- Time from end of surgery to first request for analgesia or first trigger of PCA
- Assessment of postoperative hyperalgesia in the units used in the original studies (e.g. hyperalgesia area around the surgical wound in square centimetres)
- Major and minor adverse events, as judged by the authors of the study, such as hallucinations, nightmares, dizziness, blurred vision, sedation, nausea and vomiting

Search methods for identification of studies

Electronic searches

We searched the following databases on 11 July 2018 for all relevant randomised controlled trials (RCTs) without language restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, issue 7) via CRSO to week 28;
- MEDLINE (via Ovid) 1946 to July week 28 2018;
- Embase (via Ovid) 1974 to July week 28 2018.

We used medical subject headings (MeSH) or equivalent and text word terms. We tailored the searches to the individual databases. The search strategies for CENTRAL, MEDLINE and Embase are shown in Appendix 1; Appendix 2 and Appendix 3.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), for trials that were completed but not published, and to identify any ongoing studies. In addition, we screened the reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We contacted study authors via email where necessary for additional information (e.g. for obtaining results as mean and standard deviation (SD) if data were presented as medians in the original publication).

Data collection and analysis

Selection of studies

Two review authors (ECVB and ET), independently determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria and obtained full copies of the remaining studies. Two review authors (ECVB and ET), independently read and selected relevant studies and, in the event of disagreement, a third author adjudicated (VK). We did not anonymise the studies in any way before we assessed studies for inclusion. We have included a PRISMA flow chart (Moher 2009), as recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

Data extraction and management

Two review authors (ECVB and ET), independently extracted data using a standard form and verified for agreement before entry into Review Manager 5 (RevMan 5 (Review Manager 2014)). We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. The results are summarised and interpreted in the 'Effects of interventions' section.

Assessment of risk of bias in included studies

Two review authors (ECVB and ET), independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017), and adapted from those used by the Cochrane Pregnancy and Childbirth Group. We resolved any disagreements by discussion. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan 5 (Review Manager 2014). See Characteristics of included studies.

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list or randomisation based on an individual's ID-number).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. matched in appearance); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We considered studies that were not double-blind to have high risk.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved). We excluded studies where outcome assessment was not blinded.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (10% or fewer of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis, number of participants that were excluded from the study were not reported); high risk of bias (used 'completer' analysis or inconsistency between article text and tables).
- Selective reporting (checking for reporting bias). We recorded reporting bias, such as failing to report a planned outcome. We assessed whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We assessed the methods as: low risk of bias (all predefined outcomes were reported); unclear risk of bias (insufficient information of some outcomes, e.g. only P values

were reported); high risk of bias (predefined outcomes were not reported or outcomes that were not predefined were reported.

- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

For continuous data with consistent methods of measurement (e.g. pain intensity assessed with a visual analogue scale (VAS) or another subjective, validated pain scale), we calculated mean differences (MDs). We calculated risk ratios (RR) for dichotomous outcomes that were sufficiently homogeneous to be combined (e.g. number of participants experiencing CNS adverse events or number of participants suffering from postoperative nausea and or vomiting, or both). We used random-effects models for both continuous and dichotomous outcomes. We used numbers needed to treat for an additional beneficial outcome (NNTB) and harmful outcome (NNTH), and pooled percentages as absolute measures of benefit or harm. We used 95% confidence intervals (CI) to express the uncertainty in each result.

Unit of analysis issues

We originally intended that the unit of analysis was the individual participant. We changed this to study-level data because patient-level data were only available for two studies (Joseph 2012; Lo 2008).

Dealing with missing data

We approached the corresponding authors of the included studies for missing information or data. We derived standard deviations from confidence interval data when only confidence intervals were presented. We obtained the standard deviation for each group by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size: SD = $\sqrt{N}$ x (upper limit-lower limit) / 3.92. We obtained standard deviation from the standard error of a mean if only standard errors were presented, by multiplying by the square root of the sample size: SD = SE x $\sqrt{N}$ (Higgins 2011a). We extracted means and standard deviations from graphs manually, when no numerical data were presented. Where possible and appropriate, we used intention-to-treat analyses to include all participants randomised to the study groups.

Assessment of heterogeneity

Two review authors (ECVB and ET), independently assessed the clinical homogeneity of the studies. In case of discrepancy, we consulted a third review author (VK). We used the I^2 statistic (Higgins 2003), as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, and addressed the sources of heterogeneity as appropriate (Deeks 2017).

Assessment of reporting biases

We recorded reporting bias, such as failing to report a planned outcome.

Data synthesis

We extracted both dichotomous and continuous data from the studies. We undertook a meta-analysis if we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that was clinically appropriate using a random-effects model. If the data permitted, we calculated RRs, NNTBs or NNTHs with 95% CIs. We calculated MDs for continuous data. We used RevMan 5 software for the analysis (Review Manager 2014).

When there were studies with multiple treatment arms, we excluded any arms that involved an intervention not defined by the inclusion criteria for this review. We combined data involving different ketamine regimens when there were studies with several intervention groups relevant to meta-analyses, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; table 7.7.a).

We combined intervention groups in studies investigating two intervention groups where ketamine was administered, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; table 7.7.a). We did not double-count control group participants in studies with multiple ketamine groups following guidance in Chapter 16.5.4. of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

The main analysis compared intravenous ketamine with placebo, or compared intravenous ketamine plus a basic analgesic regimen with the same basic analgesic regimen alone. The control was either placebo, or basic analgesic regimen without ketamine. This analysis was not stratified by type of surgery or any other factor, and is referred to as a non-stratified analysis. Subgroup and sensitivity analyses investigated factors such as type of surgery, study size, and pain intensity in control groups.

Quality of the evidence

Three review authors (RAM, ECVB and VKK), independently rated the quality of the evidence for each outcome using the GRADE system (GRADE 2004), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias), to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the GRADE rating by one (−1) or two (−2) if we identified:

- serious (−1) or very serious (−2) limitation to study quality;
- important inconsistency (−1);
- some (−1) or major (−2) uncertainty about directness;
- imprecise or sparse data (−1);

- high probability of reporting bias (−1).

Factors that would decrease the quality level of a body of evidence were:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, or outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- high probability of publication bias;
- imprecision beyond that expected from small studies.

We paid particular attention to inconsistency, where point estimates varied widely across studies, or CIs of studies showed minimal or no overlap (Guyatt 2011). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Nüesch 2010), while large studies often have smaller treatment effects (Dechartres 2014). We considered the consistency of results in sensitivity analyses according to study size and, where relevant, pain intensity with control when making GRADE assessments. These are circumstances in which the overall rating for a particular outcome needs to be adjusted, as recommended by GRADE guidelines (Guyatt 2013a). In circumstances where there were no data reported for an outcome, we would have reported the level of evidence as very low-quality (Guyatt 2013b).

We had planned to use GRADEpro GDT software to rank the quality of the evidence but decided not to use this tool because it does not consider study size, and because of the importance of interpreting pain levels as a key primary outcome. In order to deal with issues around size and sensitivity analyses for small-study effects with beneficial effects we created a simple grid to aid in making consistent judgements about GRADE. This is displayed in the table below. We did not use this for making GRADE decisions about adverse event data.

Amount of data (number of participants)	"Test for small-study effects (large vs small studies)"	Action	Reason
≥ 1500 participants, many studies, events common	Small-study effects absent	Do not downgrade	Large amount of data, no obvious size bias, randomness not at issue
≥ 1500 participants, many studies, events common	Small-study effects present, or not possible to test	Downgrade once, emphasise sensitivity analysis result	Large amount of data, obvious size bias, randomness not at issue
400-1499 participants, many studies, events common	Small-study effects absent	Downgrade once, limited ability of sensitivity analysis to determine small-study effects	Possible size bias and randomness effects may be present
400-1499 participants, many studies, events common	Small-study effects present, or not possible to test	Downgrade twice, emphasise sensitivity analysis result	Obvious size bias, and randomness effects may be present
≤ 400 participants, few studies, events common	Not possible to test for small-study effects	Downgrade three times	Effects of random chance large, possibility of small size bias is high

'Summary of findings' table

We included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the following outcomes:

- total consumption of opioids in milligrams of morphine equivalents for 24 and 48 hours after surgery;
- pain intensity at rest and on movement at 24 and 48 hours after surgery;
- time from end of surgery to first request for analgesia;
- postoperative hyperalgesia;
- CNS adverse events;
- postoperative nausea and vomiting.

Subgroup analysis and investigation of heterogeneity

We analysed the following predefined subgroups separately:

- studies in which ketamine had been used preoperatively or intraoperatively, or both, as well as studies where ketamine had been administered postoperatively;
- studies in which nitrous oxide had been used as a component of general anaesthesia;
- studies with benzodiazepine premedication (CNS adverse events only).

A minimum of two studies and 200 participants had to be available in any subgroup analysis, which we restricted to the primary outcomes.

Sensitivity analysis

We performed sensitivity analysis, if we identified any issues suitable for sensitivity analysis during the review process, and reported the findings as a summary table and discussed them in the review. We decided to perform sensitivity analyses for the primary outcomes. These involved both the size of studies (30 or more and 50 or more participants in treatment arms), and the amount of pain experienced, as both of these factors could influence results with data sets such as those in this review.

Study size

There is now increasing recognition that results based on a small number of small, underpowered studies may give an incorrect or highly imprecise answer to a clinical question. Studies in neuropathic pain have historically been relatively small, and analysis of smaller trials in Cochrane Reviews has been criticised (AlBalawi 2013; Roberts 2015). An analysis on the impact of study size in Cochrane Reviews has highlighted this issue, and pointed out that if two adequately powered studies are available, then omitting all underpowered studies makes little or no difference to the result (Turner 2013). The standard Cochrane 'Risk of bias' assessment does not include size, unless added by the review authors. Some items, like inconsistency or heterogeneity may be a consequence of small size (IntHout 2015; Turner 2013), but in any event, simulation studies demonstrate that the chances of heterogeneity tests accurately detecting true homogeneity or heterogeneity with a small number of small studies is almost random (Gavaghan 2000; Sterne 2000). Alternative approaches not available in RevMan 5 may offer a way forward in some circumstances (Kulinskaya 2015). There are potentially large effects of random chance when studies are small (Flather 1997; Moore 1998; Pogue 1997; Pogue 1998). A simulation exercise suggests that, in most circumstances, a minimum data requirement is 250 to 500 events, such as a participant achieving adequate pain relief (Thorlund 2011). For most pain studies where event rates are 20% to 60%, this means about 500 to 1500 participants.

Because it became clear that the studies for the review were predominantly small, with treatment group sizes of 50 participants or fewer, we decided that it was appropriate to perform a sensitivity analysis for the primary outcomes for the non-stratified results. We did this, where data allowed, for studies larger than the median group size, and for those with at least 50 participants in a treatment group. The intention was to examine the robustness of the result in such larger studies as were available.

Pain intensity

We also considered it possible that some studies would have low pain scores. Analgesic effects are difficult to measure in the absence of pain (McQuay 2012), and because of this we considered a separate sensitivity analysis for studies with at least moderate pain in the control arm, defined as 40/100 mm or more on a VAS (Collins 1997). Low pain intensity is regarded highly by people following operation (Mhuircheartaigh 2009), and generally (Moore 2013).

RESULTS

Description of studies

Results of the search

Searches of databases yielded 2222 possible hits, and we identified one further record through searching other sources. We screened 1438 studies for eligibility following duplicate removal. We discarded 1098 records based on the information given in the abstract, for example, a study investigated a paediatric population or it did not concern intravenous administration, or was presented at conferences but not published as a full journal article.

We examined 340 papers and discarded 148 because, on further examination, they did not meet our inclusion criteria. For example, the study intervention did not compare ketamine to placebo or ketamine plus basic analgesic versus basic analgesic alone (e.g. there was direct comparison between ketamine versus paracetamol), or the study investigated outcomes we were not interested in (e.g. catheter-related bladder discomfort).

We evaluated 192 full-text articles for eligibility. Three studies provided data only in units not applicable to meta-analysis or only abstracts were available (Lee 2018; Lou 2017; Moon 2018). We added these studies into 'Characteristics of studies awaiting classification', as the studies were small (fewer than 50 participants per treatment arm), and results showed that there were insufficient data to change the results and conclusion. Twenty of the studies were in Czech, Chinese, French, Korean, Russian, Spanish, or Turkish, and we assessed these with the help of native speakers or colleagues with language skills comparable to a native speaker. After excluding a further 59 (Characteristics of excluded studies), we finally included a total of 130 studies (Characteristics of included studies; Figure 1).

Figure 1. Study flow diagram

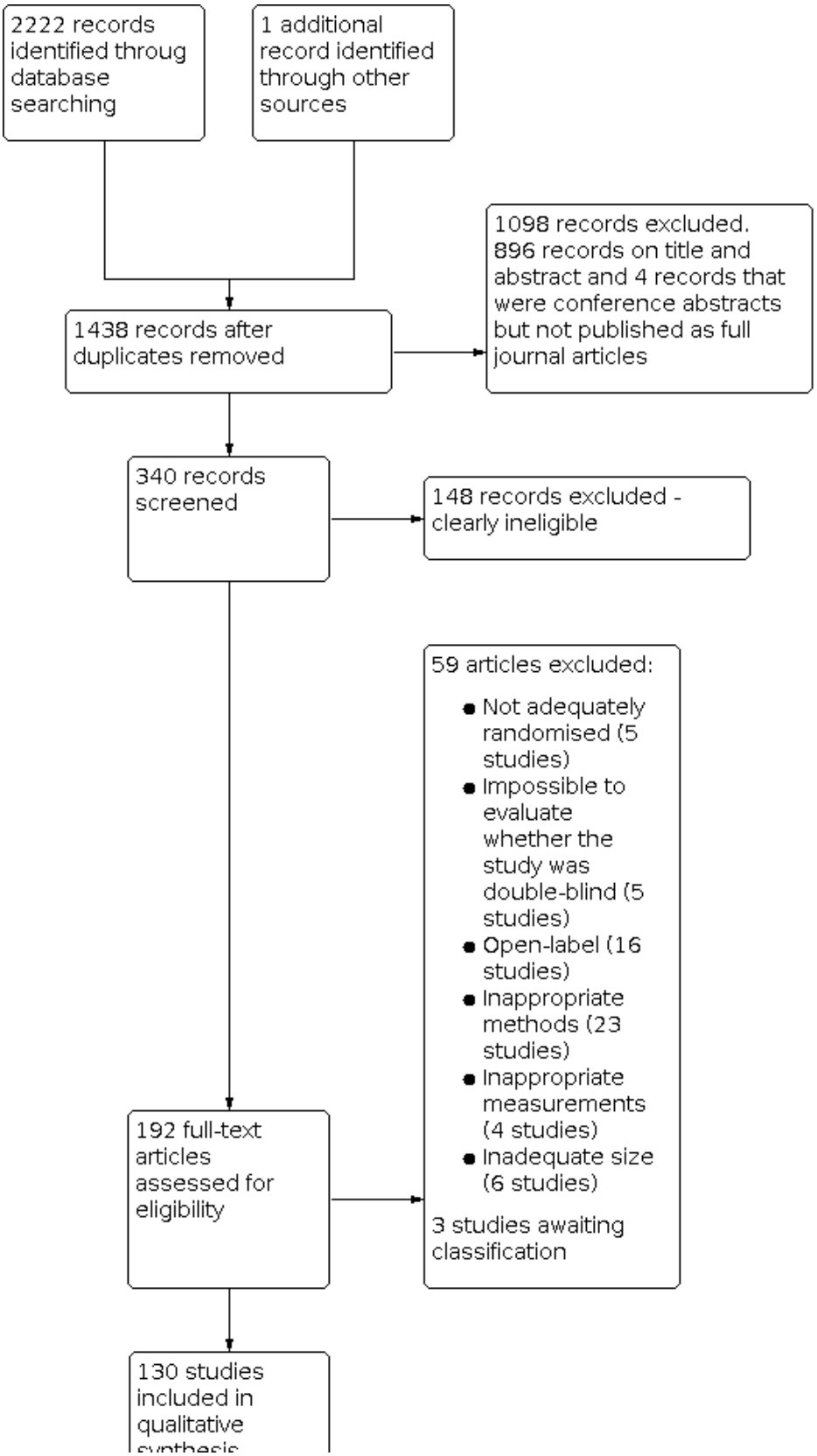
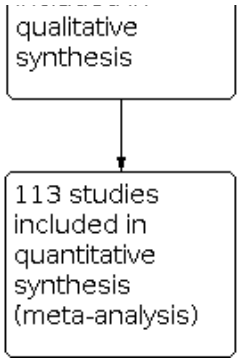


Figure 1. (Continued)



Included studies

We included 130 studies with 8341 participants. Ketamine was given to 4588 participants and 3753 received placebo or a basic analgesic alone. Ten studies investigated S-ketamine (Argiriadou 2004; Argiriadou 2011; Bornemann-Cimenti 2016; Jaksch 2002; Lahtinen 2004; Mendola 2012; Miziara 2016; Nielsen 2017; Snijdelaar 2004; Spreng 2010), one study investigated R-ketamine (Mathisen 1999), and the remaining 119 studies used racemic ketamine. Details of the included studies are in the Characteristics of included studies. Three studies comprised two treatment arms with corresponding control groups making it logical to analyse these separately for the review (Martinez 2014; Nesek-Adam 2012; Yamauchi 2008). Ayoglu 2005 reported pain intensity as VAS scores and cumulative postoperative morphine consumption up to 20 hours postoperatively. From a clinical point of view, we rounded this to 24 hours and we were able to include it in the meta-analyses.

We contacted the authors of 20 studies in order to obtain data expressed as means +/−SD. Eight authors kindly provided the necessary data. Additionally, the author of the previous Cochrane Review on this topic (and co-author of this review (RFB)) supplied data from three studies in her previous meta-analysis (Bell 2006).

Types of surgery included ear, nose or throat surgery, wisdom tooth extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, knee joint replacement surgery, anterior cruciate ligament repair of the knee, knee arthroscopy, mastectomy, haemorrhoidectomy, abdominal surgery (laparotomy and lumbotomy), radical prostatectomy, thyroid surgery, elective caesarean section and laparoscopic surgery.

Twenty-four studies administered ketamine as an intravenous bolus before incision. Eighty-four studies gave intraoperative intravenous ketamine during surgery as repeated boluses or as a continuous infusion; the infusion could stop at the end of surgery or last up to 72 hours after surgery. Sixteen studies investigated postoperative ketamine, in which ketamine was given solely in the postoperative period as a continuous infusion or via PCA. Six other studies used intravenous ketamine at more than one time, typically both before incision and around the time of wound closure (Dahl 2000; Gilabert Morell 2002; Karaman 2006; Kwok 2004; Lebrun 2006; Menigaux 2000).

Twenty-four studies did not provide results of the primary outcomes in units applicable to meta-analysis and thus contributed only to results concerning the secondary outcomes, adverse events, time to first analgesic request and hyperalgesia (Abdolahi 2013; Aqil 2011; Argiriadou 2004; Ataskhoyi 2013; Burstal 2001; Dal 2005; Dar 2012; Deng 2009; Du 2011; Galinski 2007; Hayes 2004; Kapfer 2005; Kim 2016; Köse 2012; Mebazaa MS 2008; Miziara 2016; Ong 2001; Ozhan 2013; Pacreu 2012; Pirim 2006; Siddiqui 2015; Singh 2013; Suzuki 1999; Yazigi 2012). Three other studies provided only qualitative data (Aida 2000; Colombani 2008; Lenzmeier 2008). Additionally, Aida 2000 and Lenzmeier 2008 did not report adverse events. Colombani 2008 expressed the occurrence of adverse events as a percentage of participants having any adverse event. Consequently, 113 studies provided data included in the meta-analyses.

Of the 130 studies, 23 stated that support was departmental or a grant, six declared there was no funding, three had at least some support from industry, and 98 made no mention of funding or support.

Ketamine doses used

Racemic ketamine

We found 35 studies that used a bolus dose of racemic ketamine less than 0.25 mg/kg (including Kapfer 2005, who administered a single 10 mg bolus of racemic ketamine postoperatively if opioid analgesia had not produced adequate analgesia, and Ilkjaer 1998, who administered a pre-incisional intravenous racemic ketamine bolus of 10 mg and 10 mg/hour after surgery for 48 hours). We found 15 studies that administered a bolus dose of racemic ketamine 0.3 mg/kg intravenously. We found that in 21 studies, ketamine bolus dose was 0.5 to 1 mg/kg intravenously. We found a further six studies that used racemic ketamine as a single bolus dose more than 1 mg/kg intravenously.

The other 42 studies used ketamine infusions. If administered as a continuous infusion, most studies used a rate of 2 to 5 µg/kg/min. The lowest infusion rates were 0.7 µg/kg/min (Yamauchi 2008, cervical and lumbar spine surgery), and 0.8 µg/kg/min (Aida 2000, gastrectomy and Sen 2009, total abdominal hysterectomy). Dualé 2009 administered 16 µg/kg/min during thoracotomy. Pirim 2006 started racemic ketamine infusion as high as 167 µg/kg/min for five minutes and decreased it gradually to 42 µg/kg/min which continued up to 24 hours after total abdominal hysterectomy.

S-ketamine

Of the 10 studies using S-ketamine, we found eight studies used a pre-incisional IV bolus and a continuous infusion. The bolus dose varied between 0.075 mg/kg and 0.5 mg/kg. The infusion rates for S-ketamine in these studies were 0.25 µg/kg/

min (group 1 of Bornemann-Cimenti 2016, abdominal surgery), and 1.25 µg/kg/min (Lahtinen 2004, thoracotomy), 2 µg/kg/min (Jaksch 2002, anterior cruciate ligament repair; Snijdelaar 2004, radical prostatectomy), 4.2 µg/kg/min (Nielsen 2017, lumbar fusion surgery), 5 µg/kg/min (Miziara 2016, laparoscopic cholecystectomy; Spreng 2010, ambulatory haemorrhoidectomy), and 6.7 µg/kg/min (Argiriadou 2011, thoracotomy). Argiriadou 2004 used a pre-incisional S-ketamine dose 0.5 mg/kg IV with additional S-ketamine boluses 0.2 mg/kg at 20-minute intervals during major abdominal surgery until wound closure. We found two studies that administered S-ketamine only as a continuous infusion (2 µg/kg/min and 1.7 µg/kg/min, respectively; group 2 of Bornemann-Cimenti 2016, abdominal surgery; Mendola 2012, thoracotomy).

R-ketamine

Finally, we found one study that administered R-ketamine as a single bolus 1 mg/kg IV, either pre-incisionally or at wound closure (Mathisen 1999, laparoscopic cholecystectomy).

Excluded studies

We excluded 59 studies for the following reasons:

- not adequately randomised (5 studies);
- description of methodology was deficient, for example, making it impossible to evaluate whether the study was double-blind (5 studies);
- open-label (16 studies);
- inappropriate methods (23 studies);
- inappropriate measurements (4 studies);
- inadequate size (6 studies).

See Characteristics of excluded studies.

Studies awaiting classification

We identified three recently published studies (Lee 2018; Lou 2017; Moon 2018), providing data only in units not applicable to meta-analysis or available only as abstracts. We put these studies into Characteristics of studies awaiting classification tables as the studies were small (fewer than 50 participants per treatment arm), and there were insufficient data to change the results and conclusion.

Risk of bias in included studies

Two review authors, ECVB and ET, independently assessed the risk of bias of the included studies with regard to the randomisation process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias, reporting bias, size of the study, and other potential sources of bias. A third review author (VK) resolved any discrepancy that arose in the assessment process. We have included a detailed description of risk of bias in the 'Risk of bias' tables (Characteristics of included studies). See Figure 2 for 'Risk of bias' graph and Figure 3 for 'Risk of bias' summary.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

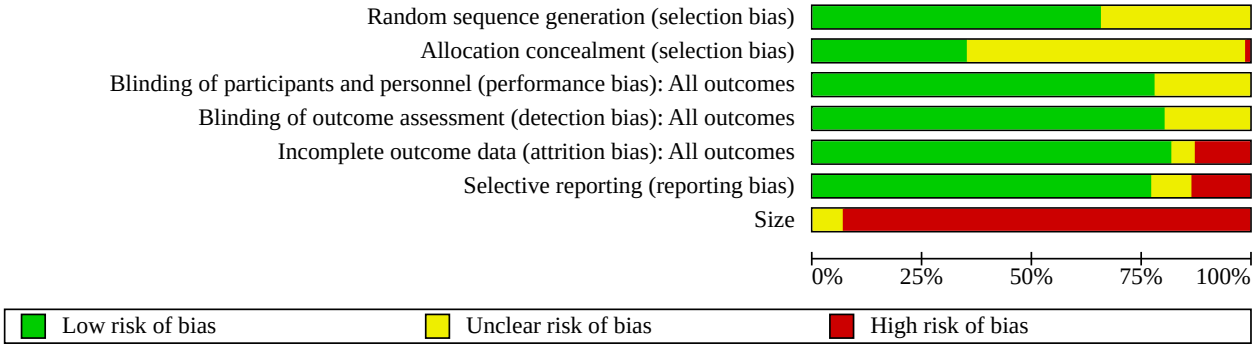


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

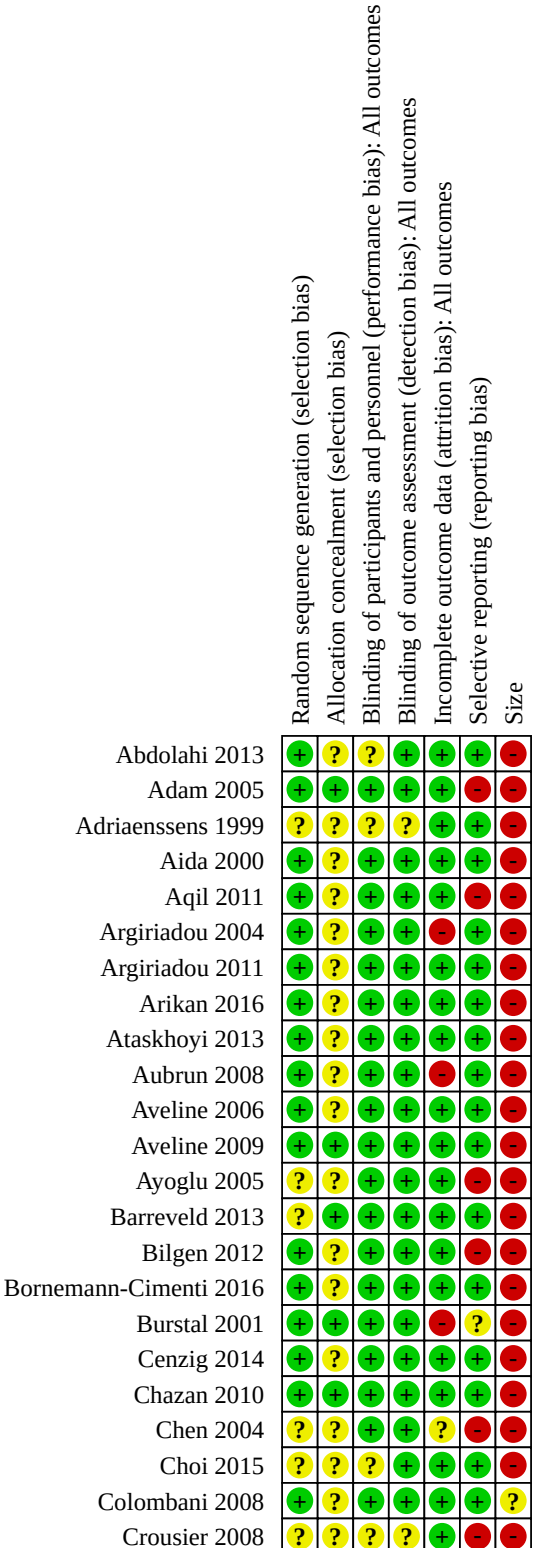
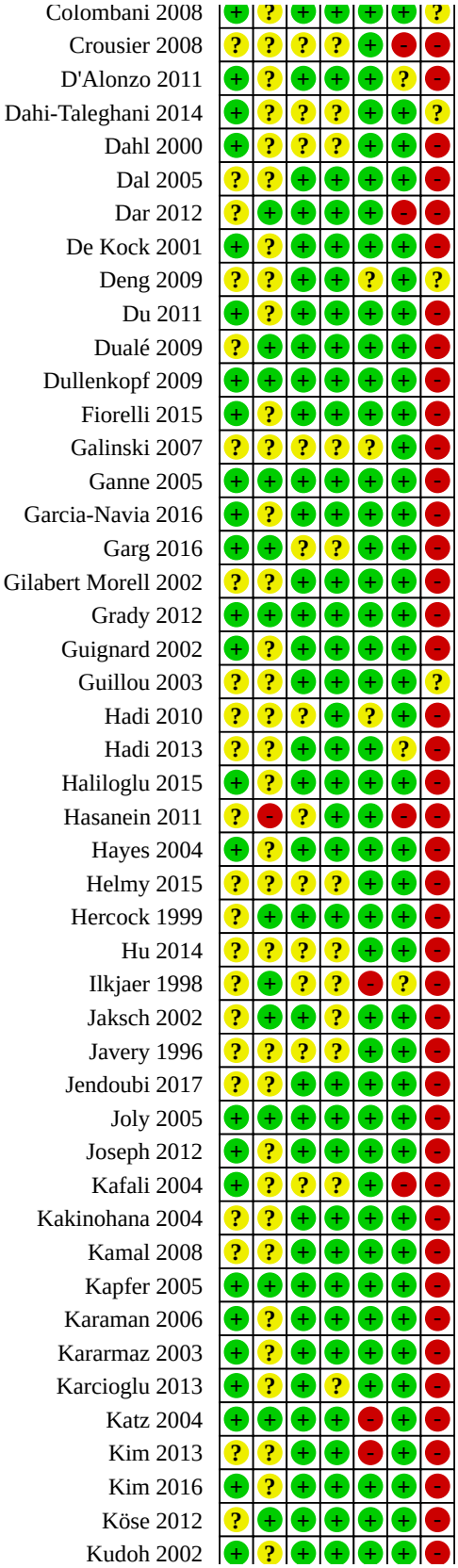


Figure 3. (Continued)



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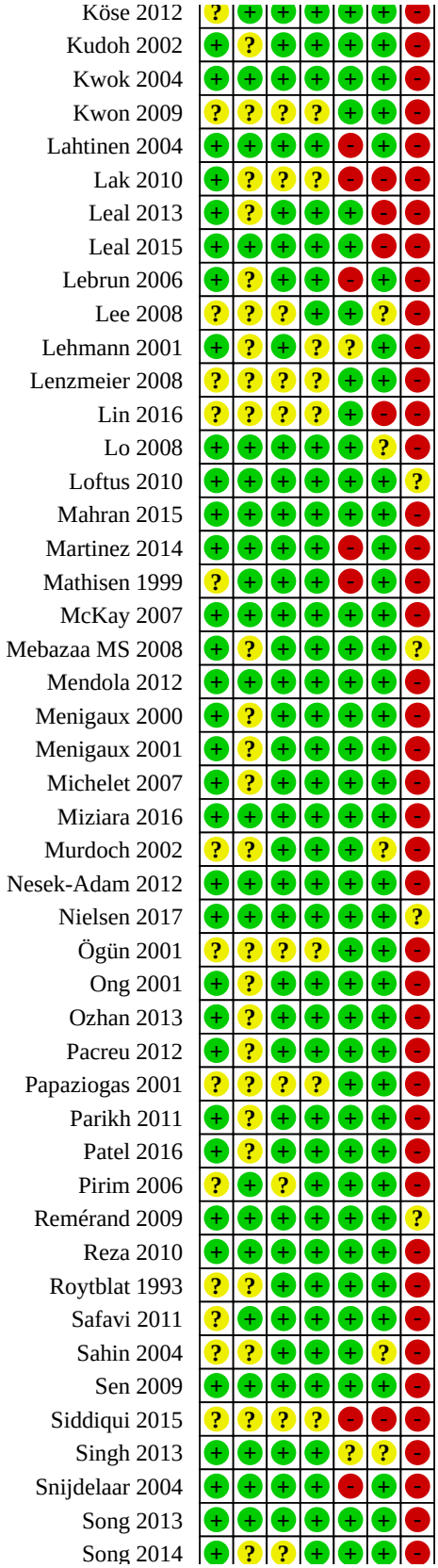
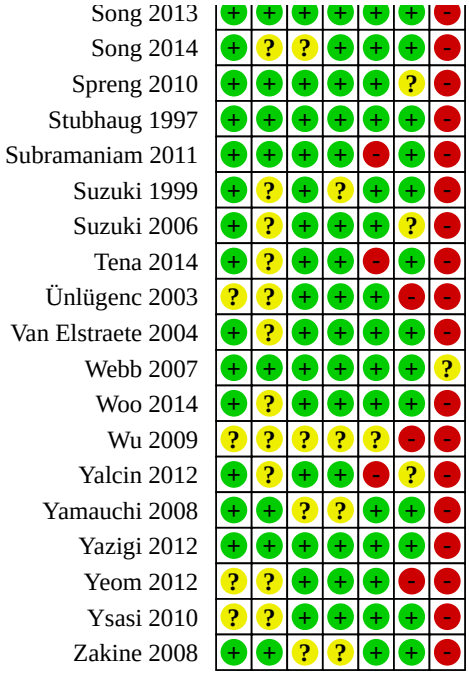


Figure 3. (Continued)



Allocation

Random sequence generation

We judged random sequence generation as adequate and the risk of bias low in 86 of the included studies. For example, we considered a computer-generated list of random numbers, shuffling envelopes or cards to be adequate sequence generation. We judged the remaining 44 studies to be at unclear risk of bias for this domain.

Allocation concealment

We regarded allocation concealment methods appropriate and the risk of bias low if the group allocation was concealed by opaque, sealed envelopes or if there was central randomisation by a third party (e.g. by a hospital pharmacy). Forty-six studies fulfilled this criteria and were at low risk of bias for this domain. Eighty-three studies did not give a detailed description of the group allocation. In this case, we judged the risk of bias concerning allocation concealment as unclear. Although we planned to exclude high risk of allocation concealment, we included Hasanein 2011 despite being judged as high risk of bias. In this study the attending anaesthesiologist was aware of the treatment allocation but study participants, and remaining personnel in the operating room and those recording data were unaware of treatment allocation. We assessed this as high risk of bias but included the study because attending anaesthesiologists did not take part in the further steps of the study.

Blinding

Blinding of participants and personnel (performance bias)

Of the 130 studies, 102 provided blinding methods in detail, allowing them to be classified as having low risk of bias concerning blinding of both participants, personnel and outcome assessment. Twenty-eight of 130 included studies were described as double-blind but did not describe the method used to achieve blinding of participants and personnel. We classified these as having unclear risk of bias. We classified Hasanein 2011 as unclear risk, as the attending anaesthetist was aware of allocation, though participants and outcome assessors were blinded.

Blinding of outcome assessment (detection bias)

The majority of studies (n = 105), reported the blinding of outcome assessment in detail and we classified them as having low risk of bias. Twenty-five of 130 included studies did not provide explicit information about how they achieved blinding of outcome assessment. We classified these studies as having unclear risk of bias. In Hasanein 2011, the attending anaesthetist was aware of treatment allocation, but as study participants and remaining personnel in the operating room and those recording data were unaware of the allocation, we regarded this as being sufficiently blinded. We therefore classified Hasanein 2011 as having unclear risk of bias.

Incomplete outcome data

In most studies (n = 107), 10% of participants or fewer failed to complete the study. We judged these to have low risk of attrition bias. Seven studies lacked adequate reporting of excluded participants and we judged their attrition bias as unclear. In fifteen studies, more than 10% of participants were excluded from the study or failed to complete. We judged their attrition bias as high. Where the exclusion rate exceeded 10%, the typical exclusion rate of participants was 11% to 13%. Burstal 2001, Lak 2010, Mathisen 1999, Subramaniam 2011 and Tena 2014 excluded 16%, 20%, 17%, 21% and 17% of study participants, respectively. Additionally, in one study (Siddiqui 2015), there was an inconsistency between the text and the table of results and we classified the study as having high risk of bias.

Selective reporting

Seventeen out of 130 studies (Adam 2005; Aqil 2011; Ayoglu 2005; Bilgen 2012; Chen 2004; Crousier 2008; Dar 2012; Hasanein 2011; Kafali 2004; Lak 2010; Leal 2013; Leal 2015; Lin 2016; Siddiqui 2015; Ünlügenc 2003; Wu 2009; Yeom 2012), either did not report outcomes predefined in the methods or published results of outcomes that were not predefined. We judged these studies as having a high risk of bias concerning selective reporting. Twelve other studies (Burstal 2001; D'Alonzo 2011; Ilkjaer 1998; Hadi 2013; Lee 2008; Lo 2008; Murdoch 2002; Sahin 2004; Singh 2013; Spreng 2010; Suzuki 2006; Yalcin 2012), provided only P values or an imprecise description of adverse events, and we judged their risk of bias for selective reporting as being unclear. In one study (Burstal 2001), the surgeon decided about the cessation of the PCA, which potentially affected this study's results concerning opioid consumption. We judged this to have unclear risk of bias concerning selective reporting. D'Alonzo 2011 reported that the anaesthetic procedure was left to the discretion of the anaesthetist and an epidural catheter was inserted when needed to control pain in a number of participants (16 in the ketamine group and 19 in the control group), so the judgement for reporting bias was unclear. Suzuki 2006 reported that the epidural infusion of morphine and ropivacaine was temporarily suspended in three participants in the ketamine group and five participants in the control group due to hypotension and we classified this study's reporting bias to be unclear. We judged the remaining studies as low risk of bias.

Other potential sources of bias

We noted that 19 studies did not report power analysis. Three trials were clearly underpowered (Crousier 2008; Lo 2008; Subramaniam 2011), and two studies (Du 2011; Köse 2012), did not base the power analysis.

Size of study

The study population was fewer than 50 participants per treatment arm in 121 studies and we judged their risk of other bias as high. Nine studies (Colombani 2008; Dahi-Taleghani 2014; Deng 2009; Guillou 2003; Loftus 2010; Mebazaa MS 2008; Nielsen 2017; Remérand 2009; Webb 2007) randomised more than 50 participants per study group and we classified their risk of other bias as unclear. We did not judge any of the studies as low risk of bias concerning study size.

The small size of studies did result in several analyses displaying high I^2 statistic values, above 90%. Such a situation is likely to arise due to random chance effects with small studies (Gavaghan 2000; Moore 1998; Sterne 2000).

Effects of interventions

See: **Summary of findings 1** Perioperative intravenous ketamine compared to placebo for acute postoperative pain in adults

We did not stratify the main analysis by type of surgery or any other factor, such as dose or timing of ketamine administration, and therefore we ran a non-stratified analysis. We conducted analyses that compared intravenous ketamine with placebo, or compared intravenous ketamine plus a basic analgesic regimen with the same basic analgesic regimen alone. The control was either placebo, or basic analgesic regimen without ketamine.

We performed sensitivity analyses in our primary analyses due to small sample sizes of studies (most had fewer than 50 participants in each treatment group), or due to considerable variation in pain levels with control. We also conducted subgroup analyses for our primary outcomes according to timing of ketamine administration, and co-administration of nitrous oxide. For CNS adverse events, we conducted a subgroup analysis relating to use of benzodiazepine premedication. These subgroup analyses follow the non-stratified analyses for the primary and secondary outcomes. We did not perform any analysis according to ketamine dose, as total doses were broadly similar and so did not allow for any sensible subgroup analysis.

Primary outcomes (non-stratified study population)

Postoperative opioid consumption

We converted to morphine equivalents using conversion equations found in the literature, if the opioid administered for postoperative analgesia was different from morphine (e.g. fentanyl, hydromorphone, oxycodone, ketobemidone, meperidine, nalbuphine, or piritramide). We used the following conversion ratios: 10:1 for IV meperidine:IV morphine (Woodhouse 1996; Pereira 2001), 1:1 for IV nalbuphine:IV morphine (Zeng 2015), 1:100 for IV fentanyl:IV morphine (Patanwala 2007), 1:5 for IV hydromorphone:IV morphine (Patanwala 2007), 2:3 for IV oxycodone:IV morphine (Anderson 2001; Silvasti 1998), 1:1 for IV ketobemidone:IV morphine (Lundeberg 2012), and 2:3 for IV piritramide:IV morphine (Kay 1971; Kumar 1999). In choosing this outcome, we recognised that we would be using opioid consumption generally reported as a mean or a median. However, neither of these is truly satisfactory, since the distribution of postoperative opioid consumption is highly skewed (Moore 2011). We have used this outcome because it is commonly reported in individual studies, and used in pooled analyses. The distribution is so skewed that mean, median, and mode are all very different to one another, though the median value appears to be more conservative in reporting lower consumption. We therefore report median and mean values where these are available.

24-hour opioid consumption in a non-stratified study population

Sixty-five studies with 4004 participants provided data for 24-hour opioid consumption postoperatively (Adriaenssens 1999; Argiriadou 2011; Aubrun 2008; Aveline 2006; Aveline 2009; Ayoglu 2005; Barreveld 2013; Bilgen 2012; Cenzig 2014; Crousier 2008; Dahi-Taleghani 2014; Dahl 2000; Dualé 2009; Dullenkopf 2009; Fiorelli 2015; Ganne 2005; Garcia-Navia 2016; Garg 2016; Gilabert Morell 2002; Guignard 2002; Guillou 2003; Hadi 2010; Hadi 2013; Haliloglu 2015; Hasanein 2011; Helmy 2015; Hercock 1999; Ilkjaer 1998; Jaksch 2002; Javery 1996; Jendoubi 2017; Kafali 2004; Kamal 2008; Karaman 2006; Katz 2004; Kwon 2009; Leal 2013; Leal 2015; Lehmann 2001; Lin 2016; Loftus 2010; Mahran 2015; Menigaux 2000; Michelet 2007; Murdoch 2002; Nielsen 2017; Ögün 2001; Parikh 2011; Remérand 2009; Reza 2010; Roytblat 1993; Safavi 2011; Sahin 2004; Sen 2009; Snijdelaar 2004; Song 2013; Song 2014; Stubhaug 1997; Subramaniam 2011; Ünlügenc 2003; Webb 2007; Woo 2014; Yalcin 2012; Ysasi 2010; Zakine 2008). Ketamine was given to 2128 participants and control to 1876. Most studies (56 of 65), had fewer than 50 participants in one treatment group; the median ketamine treatment group size was 29 participants. The median opioid consumption in control arms was 31 mg morphine equivalents (mean 42 mg).

Participants treated with ketamine consumed 7.6 mg less morphine equivalent opioid in the first 24 hours after surgery (95% CI −8.9 to −6.4; Analysis 1.1).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 participants or more. We included 2546 participants (64% of the total). In these larger studies, participants receiving ketamine consumed 7 mg less morphine equivalent opioid in the first 24 hours after surgery (95% CI −9.3 to −5.5). Using only the nine studies with ketamine treatment group size of 50 participants or more (1072 participants, 27%), the participants who received ketamine consumed 5 mg less morphine equivalent opioid in the first 24 hours after surgery (95% CI −9.9 to −0.4).

We assessed the quality of evidence for this outcome as moderate, downgraded once because the magnitude of effect fell with larger studies (small study effect) (Summary of findings 1).

Results by surgery type are shown in Summary table A.

48-hour opioid consumption in a non-stratified study population

Thirty-seven studies with 2449 participants assessed opioid consumption during the first 48 hours postoperatively (Adam 2005; Adriaenssens 1999; Argiriadou 2011; Arikan 2016; Aubrun 2008; Aveline 2009; Bilgen 2012; Bornemann-Cimenti 2016; Choi 2015; Dahl 2000; Fiorelli 2015; Ganne 2005; Garg 2016; Gilabert Morell 2002; Guillou 2003; Jaksch 2002; Kafali 2004; Kamal 2008; Kararmaz 2003; Katz 2004; Kim 2013; Kwon 2009; Lahtinen 2004; Lak 2010; Loftus 2010; Martinez 2014; Menigaux 2000; Michelet 2007; Papaziogas 2001; Remérand 2009; Snijdelaar 2004; Song 2013; Subramaniam 2011; Webb 2007; Woo 2014; Yalcin 2012; Zakine 2008). Of these, 1342 participants received ketamine while 1107 participants received control treatment. Most studies (30 of 37), had fewer than 50 participants in one treatment group; the median ketamine treatment group size was 30 participants. The median opioid consumption in control arms was 59 mg morphine equivalents (mean 67 mg).

Participants receiving ketamine consumed 12.6 mg of morphine equivalent less opioid (95% CI −15.1 to −10.2), in the first 48 hours after surgery (Analysis 1.2).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 or more (n = 1718 participants; 70% of the total). In these larger studies, we found that participants consumed 13 mg of morphine equivalent less opioid in the first 48 hours after surgery (95% CI −19 to −7.8), after ketamine administration. Using only the seven studies with ketamine treatment group size of 50 participants or more (759 participants, 30%), the participants consumed 6 mg of morphine equivalent less opioid in the first 48 hours after surgery (95% CI −11 to −0.3), after ketamine treatment.

We assessed the quality of evidence for this outcome as moderate, downgraded once because the magnitude of effect fell with larger studies (small study effect) (Summary of findings 1).

Summary table A shows results for the 24-hour and 48-hour opioid consumption data, both for all studies and according to different types of surgery. Analyses for the different types of surgery are in Appendix 4. The analyses by surgery type were not subject to any sensitivity analysis by study size or pain intensity level. In general, results by surgery type were similar to that for all surgery though in some cases there was no evidence of a difference.

Summary table A: postoperative opioid consumption 0 to 24 hours and 0 to 48 hours (data for all studies and by type of surgery)

Surgery	Studies	Participants	Morphine equivalents (mg) MD (95% CI)
Opioid consumption at 0-24 hours			
All studies	65	4004	−7.6 (−8.9 to −6.4)
Thoracotomy	4	421	−5.8 (−10.3 to −1.4)
Major orthopaedic	10	797	−19.7 (−28.6 to −10.2)
Major abdominal	16	1029	−10.3 (−13.8 to −6.8)
Total abdominal hysterectomy	9	511	−5.2 (−10.8 to 0.4)
Laparoscopic procedures	4	199	−2.7 (−6.2 to 0.8)
Opioid consumption at 0-48 hours			
All studies	37	2449	−12.6 (−15.1 to −10.2)
Thoracotomy	3	191	−12.5 (−18.3 to −6.7)
Major orthopaedic	9	557	−18.7 (−27.5 to −9.9)

Major abdominal	10	704	−14.3 (−21.2 to −7.5)
Total abdominal hysterectomy	5	378	−15.3 (−33.2 to 2.6)
Laparoscopic procedures	2	85	−4.5 (−12.2 to 3.3)

Postoperative pain intensity

Pain intensity had to be assessed using a validated measure of pain at rest and during movement (0 to 100 VAS), or other validated scale; 0 = no pain). We converted to a VAS of 0 to 100 by multiplying each reported pain score by 10 or 25, as appropriate in studies where pain intensity was assessed using a VAS of 0 to 10, a numerical rating scale (NRS) of 0 to 10, or a verbal rating scale (VRS; a 5-point scale from no pain to unbearable pain or equivalent wording).

Pain intensity at rest at 24 hours in a non-stratified study population

We found that 82 studies with 5004 participants assessed pain intensity at 24 hours (Adam 2005; Adriaenssens 1999; Argiriadou 2011; Arikan 2016; Aubrun 2008; Aveline 2006; Aveline 2009; Ayoglu 2005; Bornemann-Cimenti 2016; Cenzig 2014; Chen 2004; Choi 2015; D'Alonzo 2011; Dahi-Taleghani 2014; Dahl 2000; De Kock 2001; Dualé 2009; Fiorelli 2015; Ganne 2005; Grady 2012; Guillou 2003; Hadi 2013; Haliloglu 2015; Hercock 1999; Hu 2014; Jaksch 2002; Javery 1996; Jendoubi 2017; Joly 2005; Joseph 2012; Kafali 2004; Kakinohana 2004; Kamal 2008; Karcioglu 2013; Katz 2004; Kim 2013; Kudoh 2002; Kwok 2004; Kwon 2009; Lahtinen 2004; Lak 2010; Leal 2013; Leal 2015; Lebrun 2006; Lee 2008; Lehmann 2001; Lin 2016; Lo 2008; Loftus 2010; Mahran 2015; Mathisen 1999; Mendola 2012; Menigaux 2000; Menigaux 2001; Michelet 2007; Nesek-Adam 2012; Nielsen 2017; Ögün 2001; Papaziogas 2001; Parikh 2011; Patel 2016; Remérand 2009; Reza 2010; Safavi 2011; Sen 2009; Snijdelaar 2004; Song 2013; Spreng 2010; Subramaniam 2011; Suzuki 2006; Tena 2014; Ünlügenc 2003; Van Elstraete 2004; Webb 2007; Woo 2014; Wu 2009; Yalcin 2012; Yamauchi 2008; Yazigi 2012; Yeom 2012; Ysasi 2010; Zakine 2008). Of these, 2465 participants received ketamine and 2539 served as controls. Most studies (72 of 82) had fewer than 50 participants in one treatment group; the median ketamine treatment group size was 30 participants. The median pain score in control arms was 25/100 mm (mean 26/100 mm), and 68/82 studies had pain scores below 40/100 mm, indicating that pain was only mild in those studies.

Pain scores measured with VAS (0 to 100 mm), were 5 mm lower after ketamine treatment (95% CI −6.6 to −3.6), compared to participants receiving control treatment (Analysis 1.3).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 or more. We included 3369 participants (67% of the total), in the analysis. In these larger studies, in participants treated with ketamine, pain scores were 4 mm lower (95% CI −6.1 to −2.3).

Using only the 10 studies with ketamine treatment group size of 50 participants or more (1176 participants, 24%), in participants treated with ketamine pain scores were 5 mm lower (95% CI −8.7 to −0.6).

Pain scores for the control arms of the 82 studies varied between 4 mm and 66 mm/100 mm. Using only the 14 studies with ketamine control group pain scores of 40/100 mm or more (860 participants, 17% of the total), pain scores were 17 mm lower (95% CI −25 to −9.0), in participants treated with ketamine compared with control.

We assessed the quality of evidence for this outcome as high. We did not downgrade for small study effect because the magnitude of effect was not smaller in the larger studies (Summary of findings 1). We also had confidence because the effect of ketamine was larger in studies with higher initial pain intensity.

Results by surgery type are shown in Summary table B.

Pain intensity during movement at 24 hours in a non-stratified study population

We found 29 studies with 1806 participants that provided data for pain intensity at 24 hours during movement (Argiriadou 2011; Aveline 2009; Bornemann-Cimenti 2016; De Kock 2001; Guillou 2003; Hercock 1999; Jendoubi 2017; Joly 2005; Joseph 2012; Kakinohana 2004; Kamal 2008; Katz 2004; Kim 2013; Lahtinen 2004; Mahran 2015; Menigaux 2000; Nielsen 2017; Sen 2009; Snijdelaar 2004; Song 2013; Spreng 2010; Subramaniam 2011; Suzuki 2006; Tena 2014; Van Elstraete 2004; Webb 2007; Wu 2009; Yamauchi 2008; Yazigi 2012).

The stimulus for pain intensity during movement varied in the studies according to type of surgical procedure. Nine studies did not define the movement stimulus and used wording such as "during movement" or "at mobilization". Eight studies assessed pain during coughing, forced coughing or peak flow expiration. Two studies assessed pain during knee flexion. Two studies assessed pain on movement when the study participant rolled from supine to a side-lying position and performed two maximal inspirations. Two studies defined movement as rolling, sitting or coughing. The remaining six studies assessed pain on movement respectively when the participant tried to change position, lifted a leg when lying supine, defecated, moved a shoulder, moved to a sitting position or swallowed.

Ketamine was given to 964 participants and control to 842. Most studies (26 out of 29) had fewer than 50 participants in each study group; the median ketamine treatment group size was 30 participants. The median pain score in control arms was 43/100 mm (mean 42/100 mm), and 10 of 29 studies had pain scores below 40/100 mm, indicating that pain was only mild in those studies.

Pain scores measured with VAS (0 to 100 mm), were 6 mm lower after ketamine treatment (95% CI −10.7 to −0.5), compared to participants receiving control treatment (Analysis 1.4).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 or more. We included 1210 participants

(67% of the total), in the analysis. In these larger studies, in participants treated with ketamine, pain scores were 4 mm lower (95% CI −9.9 to −2.7).

Using only the three studies with ketamine treatment group size of 50 participants or more (395 participants, 22%), in participants treated with ketamine, pain scores were 1 mm lower (95% CI −16 to 18).

Pain scores for the control arms of the 29 studies varied between 12 mm and 69 mm/100 mm. Using the 19 studies with ketamine control group pain scores of 40/100 mm or more (1300 participants, 72%), in participants treated with ketamine, pain scores were 7 mm lower (95% CI −14 to −0.1).

We assessed the quality of evidence for this outcome as moderate, downgraded once because the magnitude of effect fell with larger studies (small study effect; Summary of findings 1).

Results by surgery type are shown in Summary table B.

Pain intensity at rest at 48 hours in a non-stratified study population

We found 49 studies with 2962 participants that provided data for pain intensity at rest at 48 hours after surgery (Adam 2005; Adriaenssens 1999; Argiriadou 2011; Arikan 2016; Aveline 2006; Aveline 2009; Bornemann-Cimenti 2016; Chazan 2010; Chen 2004; Dahl 2000; De Kock 2001; Fiorelli 2015; Ganne 2005; Grady 2012; Guillou 2003; Hu 2014; Jaksch 2002; Jendoubi 2017; Joly 2005; Joseph 2012; Kafali 2004; Kakinohana 2004; Kamal 2008; Katz 2004; Kim 2013; Kudoh 2002; Kwon 2009; Lahtinen 2004; Lak 2010; Lebrun 2006; Lo 2008; Loftus 2010; Mendola 2012; Menigaux 2000; Menigaux 2001; Michelet 2007; Papaziogas 2001; Remérand 2009; Snijdelaar 2004; Song 2013; Subramaniam 2011; Suzuki 2006; Webb 2007; Woo 2014; Wu 2009; Yamauchi 2008; Yazigi 2012; Yeom 2012; Zakine 2008). Ketamine was given to 1591 participants and control to 1371. Most studies (43 out of 49), had fewer than 50 participants in each study group; the median ketamine treatment group size was 30 participants. The median pain score in control arms was 21/100 mm (mean 23/100 mm), and 43 of 49 studies had pain scores below 40/100 mm, indicating that pain was only mild in those studies.

We found pain scores measured with VAS (0 to 100 mm), were 5 mm lower after ketamine treatment (95% CI −6.7 to −3.4) compared to participants receiving control treatment (Analysis 1.5).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 or more. We included 1972 participants (67% of the total), in the analysis. In these larger studies, in participants treated with ketamine, pain scores were 4 mm lower (95% CI −5.9 to −1.9).

Using only the seven studies with ketamine treatment group size of 50 participants or more (752 participants, 25%), in participants treated with ketamine, pain scores were 4 mm lower (95% CI −11 to 2.4).

Pain scores for the control arms of the 29 studies varied between 2 mm and 53 mm/100 mm. Using only the six studies with ketamine control group pain scores of 40/100 mm or more (359 participants, 12%), in participants treated with ketamine, pain scores were 10 mm lower (95% CI −19 to −1.1).

We assessed the quality of evidence for this outcome as high. We did not downgrade for small study effect because the magnitude of effect was not smaller in the larger studies (Summary of findings 1). We also had confidence because the effect of ketamine was larger in studies with higher initial pain intensity.

Results by surgery type are shown in Summary table B.

Pain intensity during movement at 48 hours in a non-stratified study population

Twenty-three studies with 1353 participants provided data for pain intensity during movement at 48 hours (Argiriadou 2011; Aveline 2009; Bornemann-Cimenti 2016; De Kock 2001; Guillou 2003; Jaksch 2002; Jendoubi 2017; Joly 2005; Joseph 2012; Kakinohana 2004; Kamal 2008; Katz 2004; Kim 2013; Lahtinen 2004; Menigaux 2000; Snijdelaar 2004; Song 2013; Subramaniam 2011; Suzuki 2006; Webb 2007; Wu 2009; Yamauchi 2008; Yazigi 2012).

Studies addressed pain on movement during cough or peak flow expiration (6 studies), on knee flexion (3 studies), lifting leg at supine position (1 study), rolling, sitting or coughing (2 studies), rolling from supine to side-lying position and performing two maximal inspirations (2 studies), on changing position (1 study), or did not specify movement stimulus in detail and used wording such as "during movement" or "at mobilization" (8 studies).

Ketamine was given to 739 participants and control to 614. Most studies (21 out of 23), had fewer than 50 participants in each study group; the median ketamine treatment group size was 27 participants. The median pain score in control arms was 37/100 mm (mean 37/100 mm), and 15 of 23 studies had pain scores below 40/100 mm, indicating that pain was only mild in those studies.

Pain scores measured with VAS (0 to 100 mm), were 6 mm lower after ketamine treatment (95% CI −10.2 to −1.3) compared to participants receiving control treatment (Analysis 1.6).

Sensitivity analyses

We performed a sensitivity analysis using only those studies with a treatment group size of 30 or more. We included 853 participants (63% of the total), in the analysis. In these larger studies, in participants treated with ketamine, pain scores were 5 mm lower (95% CI −11 to 0.8).

Using only the two studies with ketamine treatment group size of 50 participants or more (250 participants, 18%), we found participants treated with ketamine pain scores were 2 mm higher (95% CI −14 to 17).

Pain scores for the control arms of the 23 studies varied between 5 mm and 70 mm/100 mm. We found eight studies with ketamine control group pain scores of 40/100 mm or more (379 participants, 28%), in participants treated with ketamine, pain scores were 10 mm lower (95% CI −14 to −6.1).

We assessed the quality of evidence for this outcome as low, downgraded once because the magnitude of effect fell with larger studies (small study effect), and once because there were fewer than 1500 participants in the analysis (Summary of findings 1).

Summary table B shows results for the 24-hour and 48-hour pain intensity data at rest and during movement, both for all studies and according to different types of surgery. The detailed results for

these are in Appendix 5. The analyses by surgery type were not subject to any sensitivity analysis by study size or pain intensity level. In general, results by surgery type were similar to that for all surgery though in some cases there was no evidence of a difference.

(data for all studies (non-stratified) and stratified by type of surgery)

Surgery	Studies	Participants	VAS 0-100 (mm) MD (95% CI)
Pain at rest at 24 hours			
All studies	82	5004	−5 (−6.6 to −3.6)
Thoracotomy	13	782	−4 (−8.8 to 1.0)
Major orthopaedic	11	843	−6 (−9.9 to −3.0)
Major abdominal	18	1178	−7 (−11 to −4.2)
Total abdominal hysterectomy	8	493	−3 (−4.6 to −0.5)
Laparoscopic procedures	9	484	−2 (−6.7 to 2.0
Pain during movement at 24 hours			
All studies	29	1806	−6 (−11 to −0.5)
Thoracotomy	5	315	−7 (−20 to 5.5)
Major orthopaedic	4	279	−7 (−12 to −0.8)
Major abdominal	9	666	−3 (−11 to 5.7)
Total abdominal hysterectomy	no data		
Laparoscopic procedures	no data		
Pain at rest at 48 hours			
All studies	49	2962	−5 (−6.7 to −3.4)
Thoracotomy	9	530	−7 (−10 to −3.4)
Major orthopaedic	7	453	−1 (−4.1 to 1.3)
Major abdominal	13	891	−6 (−8.9 to −3.1)
Total abdominal hysterectomy	no data		
Laparoscopic procedures	no data		
Pain during movement at 48 hours			
All studies	23	1353	−6 (−10 to −1.3)
Thoracotomy	5	298	−11 (−15 to −6.0)
Major orthopaedic	4	157	−7 (−13 to −1.6)

Major abdominal	9	662	−3 (−9.2 to 3.3)
Total abdominal hysterectomy	no data		
Laparoscopic procedures	no data		

Secondary outcomes (non-stratified study population)

Time to first analgesic request

We found 31 studies with 1678 participants that provided data on how ketamine affects the time to first analgesic request (Adam 2005; Aqil 2011; Ataskhoyi 2013; Aveline 2009; Cenzig 2014; Choi 2015; Dal 2005; Dar 2012; Gilabert Morell 2002; Hadi 2010; Hadi 2013; Helmy 2015; Jaksch 2002; Kafali 2004; Kakinohana 2004; Karaman 2006; Kararmaz 2003; Köse 2012; Lahtinen 2004; Leal 2013; Lin 2016; Menigaux 2000; Nesek-Adam 2012; Ong 2001; Papaziogas 2001; Parikh 2011; Roytblat 1993; Safavi 2011; Sahin 2004; Song 2014; Ysasi 2010). These studies included trials where ketamine was administered pre- or intraoperatively but not after surgery. The median time to first request with control was 18 minutes (mean 39 minutes).

We found that 933 participants who received ketamine requested analgesia a mean of 54 minutes later (95% CI 37 to 71), than 745 participants in the control group (Analysis 1.7). A single study reported an extraordinary increase of over 1000 minutes (Parikh 2011). Omitting this still provided evidence of a difference with an increase of 22 minutes (95% CI 15 to 29).

We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once because we could not test for small-study effects despite there being more than 1500 participants in the analysis (Summary of findings 1).

Studies assessing postoperative hyperalgesia

We found seven studies with 333 participants (Bornemann-Cimenti 2016 Burstal 2001; De Kock 2001; Joly 2005; Leal 2015; Song 2014; Stubhaug 1997), providing data for hyperalgesia assessed at 24 hours postoperatively. They expressed results as area of hyperalgesia. We were able to derive the area as square centimetres in two studies (Joly 2005; Leal 2015). In three studies mean values for affected area were smaller than the SD for treatment, control, or both groups (158 participants, 47% of total; Bornemann-Cimenti 2016; Burstal 2001; De Kock 2001). Only two of 14 treatment groups involved 30 participants or more.

Overall 188 participants received ketamine and 145 received control treatment. The area of hyperalgesia for those receiving control treatment was 15 cm^2. Ketamine treatment reduced the area of postoperative hyperalgesia by 7 cm^2 (95% CI −11.9 to −2.2; Analysis 1.9).

We assessed the quality of evidence for this outcome as very low. We downgraded the quality of evidence three times to very low because there were fewer than 400 participants in the analysis (Summary of findings 1).

Bornemann-Cimenti 2016 assessed hyperalgesia after major abdominal surgery. In this study, ketamine administration lasted up to 48 hours after surgery along with a PCA device administering piritramide. Burstal 2001 administered ketamine via PCA after abdominal hysterectomy. Participants also received analgesia via epidural catheter. De Kock 2001 and Joly 2005 investigated ketamine during major abdominal surgery. Participants received ketamine as a pre-incisional bolus followed by an infusion that lasted up to 48 hours after surgery. Leal 2015 and Song 2014 administered ketamine intraoperatively during laparoscopic procedures along with remifentanil infusion. Remifentanil is known for its hyperalgesic effect. Stubhaug 1997 administered ketamine as a pre-incisional bolus followed by infusion that lasted up to 48 hours after nephrectomy. Participants also received intercostal nerve blockades.

Adverse events with ketamine

Because reports did not categorise adverse events as major or minor, we pooled all adverse event reports together, and report hallucination, dizziness, confusion, drowsiness, sedation, nightmares and visual disturbances separately from postoperative nausea and vomiting.

Central nervous system (CNS) adverse events

For this analysis, we pooled all CNS adverse events (hallucination, dizziness, confusion, drowsiness, sedation, nightmares and visual disturbances). One hundred and five studies with 6538 participants provided dichotomous data on CNS adverse events. Twelve studies (742 participants) did not report on CNS adverse events (Aida 2000; Choi 2015; Dahl 2000; Dahi-Taleghani 2014; Grady 2012; Helmy 2015; Kakinohana 2004; Ong 2001; Patel 2016; Song 2014; Ünlügenc 2003; Yalcin 2012).

We found 53 studies (2832 participants), that reported that no CNS adverse events occurred in either study group (Adam 2005; Adriaenssens 1999; Argiriadou 2004; Argiriadou 2011; Ataskhoyi 2013; Aveline 2009; Chen 2004; D'Alonzo 2011; Dal 2005; De Kock 2001; Du 2011; Fiorelli 2015; Ganne 2005; Garcia-Navia 2016; Gilabert Morell 2002; Guignard 2002; Hadi 2010; Hadi 2013; Haliloglu 2015; Hasanein 2011; Hercock 1999; Jaksch 2002; Jendoubi 2017; Kafali 2004; Karaman 2006; Karcioglu 2013; Kim 2013; Köse 2012; Kwok 2004; Kwon 2009; Lebrun 2006; Lehmann 2001; Lin 2016; Mahran 2015; Mathisen 1999; Mendola 2012; Menigaux 2000; Menigaux 2001; Michelet 2007; Pacreu 2012; Papaziogas 2001; Parikh 2011; Pirim 2006; Roytblat 1993; Sahin 2004; Snijdelaar 2004; Spreng 2010; Suzuki 1999; Van Elstraete 2004; Woo 2014; Yeom 2012; Ysasi 2010; Zakine 2008).

We found 52 studies (3706 participants), that reported CNS adverse events (Aqil 2011; Arikan 2016; Aubrun 2008; Aveline 2006; Ayoglu 2005; Barreveld 2013; Bilgen 2012; Burstal 2001; Cenzig 2014; Chazan 2010; Deng 2009; Dualé 2009; Dullenkopf 2009; Galinski 2007; Garg 2016; Guillou 2003; Hayes 2004; Hu 2014; Ilkjaer 1998; Joly 2005; Joseph 2012; Kamal 2008; Kapfer 2005; Kararmaz 2003; Katz 2004; Kim 2016; Kudoh 2002; Lahtinen 2004; Lak 2010; Leal 2013; Leal 2015; Lo 2008; Loftus 2010; Martinez 2014; McKay 2007;

Mebazaa MS 2008; Miziara 2016; Nesek-Adam 2012; Nielsen 2017; Remérand 2009; Reza 2010; Safavi 2011; Sen 2009; Siddiqui 2015; Singh 2013; Song 2013; Subramaniam 2011; Tena 2014; Webb 2007; Wu 2009; Yalcin 2012; Yazigi 2012).

Combining both of these groups, we found that studies had observed CNS adverse events in 187 of 3614 (5%), participants receiving ketamine compared to 122 of 2924 (4%), participants receiving control treatment. The RR was 1.17 (95% CI 0.95 to 1.43; Analysis 1.8).

We assessed the quality of evidence for this outcome as high due to consistency across a large body of data. Studies did not note any CNS adverse events in 53 studies with 43% of participants, and the other studies had low rates of CNS adverse events (Summary of findings 1). In the studies that reported at least one CNS adverse event, there was also no evidence of a difference between ketamine and placebo, with RR 1.17 (95% CI 0.95 to 1.43; Analysis 1.10).

In addition, four studies reported CNS adverse events as continuous data, using a specific score (Bornemann-Cimenti 2016; Stubhaug 1997; Suzuki 2006; Yamauchi 2008). Bornemann-Cimenti 2016 assessed postoperative delirium using the Intensive Care Delirium Screening Checklist (ICDSC). The ICDSC score was increased in the low-dose ketamine study group (ketamine 0.25 mg/kg bolus and 0.125 mg/kg/h infusion for 48 hours), compared with the minimal-dose ketamine group (a 0.015 mg/kg/h infusion), and the placebo group. In the remaining three studies, there was no difference in the degree of CNS adverse events between treatment and control groups.

Six studies reported the number of participants withdrawn from the study because of CNS adverse events (Burstal 2001; Joseph 2012; Lahtinen 2004; Song 2013; Subramaniam 2011; Webb 2007). For all studies reporting the outcome of CNS adverse event withdrawal, 12 of 5884 (0.2%), participants having ketamine were withdrawn, and 3 of 3447 (0.09%), participants with control.

Postoperative nausea and vomiting

We combined the data concerning nausea and vomiting, or both. Four studies reported that postoperative nausea and vomiting did not occur in either study group (Fiorelli 2015; Galinski 2007; Helmy 2015; Menigaux 2001).

Ninety-five studies with 5965 participants provided dichotomous data on nausea and vomiting, or nausea, or vomiting. In 91 studies postoperative nausea and vomiting occurred in both study groups (Abdolahi 2013; Adriaenssens 1999; Aqil 2011; Argiriadou 2004; Arikan 2016; Ataskhoyi 2013; Aubrun 2008; Aveline 2006; Aveline 2009; Ayoglu 2005; Bilgen 2012; Cenzig 2014; Chazan 2010; Crousier 2008; Dahi-Taleghani 2014; Dal 2005; Dar 2012; Deng 2009; Dualé 2009; Garcia-Navia 2016; Garg 2016; Gilabert Morell 2002; Grady 2012; Guignard 2002; Guillou 2003; Hadi 2013; Haliloglu 2015; Hasanein 2011; Hu 2014; Jaksch 2002; Jendoubi 2017; Joly 2005; Joseph 2012; Kafali 2004; Kakinohana 2004; Kamal 2008; Kapfer 2005; Karaman 2006; Kararmaz 2003; Kim 2013; Kim 2016; Köse 2012; Kwok 2004; Kwon 2009; Lahtinen 2004; Lak 2010; Leal 2013; Leal 2015; Lehmann 2001; Lin 2016; Lo 2008; Loftus 2010; Mahran 2015; Martinez 2014; McKay 2007; Mebazaa MS 2008; Mendola 2012; Menigaux 2000; Michelet 2007; Miziara 2016; Nesek-Adam 2012; Nielsen 2017; Ögün 2001; Ong 2001; Ozhan 2013; Pacreu 2012; Papaziogas 2001; Parikh 2011; Pirim 2006; Remérand 2009; Reza 2010; Roytblat 1993; Safavi 2011; Sen 2009; Siddiqui 2015; Singh 2013; Snijdelaar 2004; Song 2013; Spreng 2010; Stubhaug 1997; Subramaniam 2011; Suzuki 1999; Tena 2014; Ünlügenc 2003; Van Elstraete 2004; Woo 2014; Wu 2009; Yazigi 2012; Yeom 2012; Ysasi 2010; Zakine 2008).

In the 95 studies 761 of 3263 (23%), participants who received ketamine and 731 of 2702 (27%), participants who received control treatment suffered from postoperative nausea and vomiting. Ketamine treatment reduced the incidence of postoperative nausea and vomiting (RR 0.88, 95% CI 0.81 to 0.96; Analysis 1.11). We calculated that the NNTB to prevent one episode of postoperative nausea and vomiting with perioperative intravenous ketamine administration was 24 (95% CI 16 to 54).

We assessed the quality of evidence for this outcome as high due to consistency across a large body of data (Summary of findings 1).

Subgroup analyses of primary and secondary outcomes

We carried out a number of subgroup analyses to investigate factors that may have influenced the overall results. We used analyses that compared intravenous ketamine with placebo, or compared intravenous ketamine plus a basic analgesic regimen with the same basic analgesic regimen alone using a non-stratified study population.

Subgroup analysis of pre-incisional and postoperative ketamine

24-hour opioid consumption

We found 19 studies that administered ketamine as a pre-incisional bolus at the beginning of surgery and reported 24-hour opioid consumption (Argiriadou 2011; Aveline 2006; Bilgen 2012; Cenzig 2014; Dahl 2000; Dullenkopf 2009; Fiorelli 2015; Garcia-Navia 2016; Gilabert Morell 2002; Helmy 2015; Kafali 2004; Karaman 2006; Kwon 2009; Lehmann 2001; Menigaux 2000; Reza 2010; Roytblat 1993; Sahin 2004; Song 2013). The studies included 573 participants who received ketamine and 472 participants who received control treatment. Pre-incisionally administered ketamine reduced 24-hour opioid consumption by 5.5 mg morphine equivalents compared with control (95% CI −8.0 to −3.1; Analysis 2.1). We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once from high to moderate because studies were small and because we could not test for small-study effects (18 of the 19 studies included in this analysis had fewer than 50 participants in each treatment group).

We found nine studies that administered ketamine in the postoperative period and reported 24-hour opioid consumption (Adriaenssens 1999; Barreveld 2013; Dahi-Taleghani 2014; Garg 2016; Guillou 2003; Javery 1996; Kamal 2008; Michelet 2007; Ünlügenc 2003). We found 293 participants who received ketamine and 301 participants who received control treatment. Ketamine treatment reduced opioid consumption at 24 hours by 9 mg morphine equivalents compared with control (95% CI −13.8 to −3.5; Analysis 2.1). We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once from high to moderate because studies were small and because we could not test for small-study effects (all studies included in this analysis had fewer than 50 participants in each treatment group).

The test for difference (Analysis 2.1), showed no evidence of a difference (P = 0.28).

48-hour opioid consumption

We found nine studies that administered ketamine as a pre-incisional bolus and reported opioid consumption at 48 hours after surgery (Bilgen 2012; Dahl 2000; Fiorelli 2015; Gilabert Morell 2002; Kafali 2004; Kwon 2009; Menigaux 2000; Papaziogas 2001; Song 2013). We found that 305 participants received ketamine and 229 participants received control treatment. Pre-incisionally administered ketamine reduced opioid consumption at 48 hours by 3.9 mg morphine equivalents, compared with control (95% CI −7.0 to −0.7; Analysis 2.2). We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once from high to moderate because studies were small and because we could not test for small-study effects (all studies included in this analysis had fewer than 50 participants in each treatment group).

We found seven studies that administered ketamine in the postoperative period and reported 48-hour opioid consumption (Adriaenssens 1999; Arikan 2016; Garg 2016; Guillou 2003; Kamal 2008; Lak 2010; Michelet 2007). We found 207 participants who received ketamine and 218 participants who received control treatment. Ketamine treatment reduced opioid consumption at 48 hours by 21 mg morphine equivalents compared with control (95% CI −27.4 to −14.2; Analysis 2.2). We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once from high to moderate because studies were small and because we could not test for small-study effects (all studies included in this analysis had fewer than 50 participants in each treatment group).

The test for difference (Analysis 2.2) showed evidence of a difference between pre-incisional and postoperative ketamine (P = 0.000001).

Pain intensity at 24 hours

We found 20 studies that administered ketamine as a pre-incisional bolus and reported pain intensity at 24 hours after surgery (Aveline 2006; Cenzig 2014; D'Alonzo 2011; Dahl 2000; Fiorelli 2015; Kafali 2004; Kwok 2004; Kwon 2009; Lebrun 2006; Lee 2008; Lehmann 2001; Mathisen 1999; Menigaux 2000; Menigaux 2001; Nesek-Adam 2012; Papaziogas 2001; Patel 2016; Reza 2010; Roytblat 1993; Safavi 2011). Five hundred and sixty-four participants received ketamine and 511 participants received control treatment. Pain intensity was 7 mm lower (95% CI −10.1 to −3.2), among participants who received ketamine compared to controls (Analysis 2.3). We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (19 of the 20 studies included in this analysis had fewer than 50 participants in each treatment group).

We found nine studies that administered ketamine postoperatively and reported pain intensity at 24 hours after surgery (Adriaenssens 1999; Dahi-Taleghani 2014; Guillou 2003; Javery 1996; Kamal 2008; Lak 2010; Lo 2008; Michelet 2007; Ünlügenc 2003). We found that 282 participants received ketamine and 289 participants received control treatment. Pain intensity was 8 mm lower among participants who received ketamine compared with control (95% CI −12.6 to −4.1; Analysis 2.3). We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (eight of the nine studies included in this analysis had fewer than 50 participants in each treatment group).

The test for difference (Analysis 2.3) showed no evidence of a difference (P = 0.55).

Pain intensity at 48 hours

We found nine studies that administered ketamine as a pre-incisional bolus and reported pain intensity at 48 hours after surgery (Aveline 2006; Dahl 2000; Fiorelli 2015; Kafali 2004; Kwon 2009; Lebrun 2006; Menigaux 2000; Menigaux 2001; Papaziogas 2001). We found 282 participants received ketamine and 227 participants received control treatment. Ketamine treatment lowered reduced pain intensity by 4 mm (95% CI −7.5 to −1.2), compared with controls (Analysis 2.4). We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (eight of the nine studies included in this analysis had fewer than 50 participants in each treatment group).

We found six studies that administered ketamine postoperatively and reported pain intensity at 48 hours after surgery (Adriaenssens 1999; Guillou 2003; Kamal 2008; Lak 2010; Lo 2008; Michelet 2007). We found 160 participants who received ketamine and 171 participants who received control treatment. Pain intensity measured as VAS was 8 mm lower among participants who received ketamine compared with control (95% CI −15.8 to −0.3; Analysis 2.4). We assessed the quality of evidence for this outcome as very low. We downgraded the quality of evidence three times from high to very low because there were fewer than 400 participants in the analysis.

The test for difference (Analysis 2.4) showed no evidence of a difference (P = 0.39).

Time to first request for analgesia after pre-incisional ketamine administration

We found 13 studies where ketamine was administered pre-incisionally that reported time to first request for analgesia (Aqil 2011; Ataskhoyi 2013; Cenzig 2014; Gilabert Morell 2002; Helmy 2015; Kafali 2004; Menigaux 2000; Nesek-Adam 2012; Ong 2001; Papaziogas 2001; Roytblat 1993; Safavi 2011; Sahin 2004). We found 352 participants who received ketamine and 291 participants who received control treatment. Ketamine administration delayed time to first request for analgesia by a mean of 38 minutes (95% CI 20.9 to 54.5; Analysis 2.5). We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (12 of the 13 studies included in this analysis had fewer than 50 participants in each treatment group).

We found no studies for postoperative ketamine.

Effect of co-administration of ketamine and nitrous oxide

We conducted separate analyses of studies where ketamine was administered together with nitrous oxide. Nitrous oxide did not seem to change the effect of ketamine.

24-hour opioid consumption

Thirty-three studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Adriaenssens 1999; Aveline 2006; Aveline 2009; Bilgen 2012; Cenzig 2014; Crousier 2008; Dahi-Taleghani 2014; Dahl 2000; Dullenkopf 2009; Garg 2016; Gilabert Morell 2002; Grady 2012; Guillou 2003; Hadi 2010; Hadi 2013; Haliloglu 2015; Hercock 1999; Karaman 2006; Katz 2004; Leal 2013; Lehmann 2001; Menigaux 2000; Murdoch 2002; Ögün 2001; Parikh 2011; Remérand 2009; Reza 2010; Roytblat 1993; Safavi 2011; Sahin 2004; Sen 2009; Ünlügenc 2003; Zakine 2008). There were 1247 participants who received ketamine and 929 participants who received control treatment. Ketamine administration reduced postoperative opioid consumption at 24 hours by 7 mg morphine equivalents compared with control (95% CI −9.8 to −4.8; Analysis 3.1).

We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (27 of the 33 studies included in this analysis had fewer than 50 participants in each treatment group).

48-hour opioid consumption

Fifteen studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Adam 2005; Adriaenssens 1999; Arikan 2016; Aveline 2009; Bilgen 2012; Dahl 2000; Garg 2016; Guillou 2003; Katz 2004; Kim 2013; Lak 2010; Menigaux 2000; Remérand 2009; Snijdelaar 2004; Zakine 2008). There were 657 participants who received ketamine and 453 participants who received control treatment. Ketamine administration reduced postoperative opioid consumption by 15 mg morphine equivalents compared with control (95% CI −21.1 to −8.4; Analysis 3.2).

We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (13 of the 15 studies included in this analysis had fewer than 50 participants in each treatment group).

Pain intensity at rest at 24 hours

Thirty-two studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Adam 2005; Adriaenssens 1999; Arikan 2016; Aubrun 2008; Aveline 2006; Aveline 2009; Cenzig 2014; Dahl 2000; Guillou 2003; Hadi 2010; Haliloglu 2015; Hercock 1999; Katz 2004; Kim 2013; Kwok 2004; Lak 2010; Lee 2008; Lehmann 2001; Menigaux 2000; Menigaux 2001; Ögün 2001; Parikh 2011; Remérand 2009; Reza 2010; Safavi 2011; Sen 2009; Snijdelaar 2004; Suzuki 2006; Ünlügenc 2003; Yamauchi 2008; Yeom 2012; Zakine 2008). There were 1145 participants who received ketamine and 908 participants who received control treatment. Pain intensity measured as VAS was 8 mm lower among participants who had received ketamine compared with control (95% CI −10.8 to −5.4; Analysis 3.3).

We assessed the quality of evidence for this outcome as moderate. We downgraded the quality of evidence once from high to moderate because we could not test for small-study effects despite there being more than 1500 participants in the analysis (26 of the 31 studies included in this analysis had fewer than 50 participants in each treatment group).

Pain intensity during movement at 24 hours

Ten studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Aveline 2009; Guillou 2003; Hercock 1999; Katz 2004; Kim 2013; Menigaux 2000; Sen 2009; Snijdelaar 2004; Suzuki 2006; Yamauchi 2008). There were 354 participants who received ketamine and 259 participants who received control treatment. Pain intensity measured as VAS at 24 hours during movement was 7 mm lower (95% CI −19.0 to 6.0), after ketamine administration compared with control (Analysis 3.4).

We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (nine of the 10 studies included in this analysis had fewer than 50 participants in each treatment group).

Pain intensity at rest at 48 hours

Eighteen studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Adam 2005; Adriaenssens 1999; Arikan 2016; Aveline 2006; Aveline 2009; Dahl 2000; Guillou 2003; Katz 2004; Kim 2013; Lak 2010; Menigaux 2000; Menigaux 2001; Remérand 2009; Snijdelaar 2004; Suzuki 2006; Yamauchi 2008; Yeom 2012; Zakine 2008). There were 689 participants who received ketamine and 513 participants who received control treatment. Pain intensity measured as VAS at rest at 48 hours was 6 mm lower after ketamine administration compared with control (95% CI −9.9 to −2.8; Analysis 3.5).

We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (14 of the 18 studies included in this analysis had fewer than 50 participants in each treatment group).

Pain intensity during movement at 48 hours

Eight studies administered ketamine where nitrous oxide was used as a component of general anaesthesia (Aveline 2009; Guillou 2003; Katz 2004; Kim 2013; Menigaux 2000; Snijdelaar 2004; Suzuki 2006; Yamauchi 2008). There were 310 participants who received ketamine and 213 participants who received control treatment. Pain intensity measured as VAS at 48 hours during movement was 5 mm lower after ketamine administration compared with control (95% CI −13.1 to 4.1; Analysis 3.6).

We assessed the quality of evidence for this outcome as low. We downgraded the quality of evidence twice from high to low, once because there were fewer than 1500 participants in the analysis and once because we could not test for small-study effects (fewer than 50 participants in each treatment group).

Effect of co-administration of benzodiazepine premedication

CNS adverse events

We found 65 studies (3943 participants), that used benzodiazepine premedication before ketamine administration.

Thirty-four studies (1739 participants), did not find any CNS adverse events (Adam 2005; Adriaenssens 1999; Argiriadou 2004; Argiriadou 2011; Ataskhoyi 2013; Aveline 2009; De Kock 2001; Fiorelli 2015; Ganne 2005; Garcia-Navia 2016; Gilabert Morell 2002; Guignard 2002; Hadi 2010; Hadi 2013; Hasanein 2011; Jaksch 2002; Jendoubi 2017; Kwon 2009; Lebrun 2006; Lehmann 2001; Mahran 2015; Mathisen 1999; Mendola 2012; Menigaux 2000; Menigaux 2001; Michelet 2007; Pacreu 2012; Papaziogas 2001; Pirim 2006; Roytblat 1993; Snijdelaar 2004; Suzuki 1999; Van Elstraete 2004; Zakine 2008).

Thirty-one studies (2204 participants), reported CNS adverse events after benzodiazepine premedication (Aqil 2011; Arikan 2016; Aubrun 2008; Aveline 2006; Chazan 2010; Dualé 2009; Dullenkopf 2009; Galinski 2007; Garg 2016; Guillou 2003; Hayes 2004; Hu 2014; Ilkjaer 1998; Joly 2005; Joseph 2012; Kamal 2008; Kararmaz 2003; Katz 2004; Kim 2016; Leal 2013; Loftus 2010; Martinez 2014; Mebazaa MS 2008; Remérand 2009; Sen 2009; Siddiqui 2015; Singh 2013; Subramaniam 2011; Tena 2014; Yalcin 2012; Yazigi 2012).

These trials reported CNS adverse events in 123 of 2179 (5.6%), participants treated with ketamine and 91 of 1764 (5.2%), participants receiving control. The RR was 1.1 (95% CI 0.9 to 1.4; Analysis 4.1). This was very similar to the result overall.

We assessed the quality of evidence for this outcome as high.

DISCUSSION

Summary of main results

The aim of this review was to evaluate the efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia.

We included 130 studies (8341 participants) in the review. Of these, 4588 participants received ketamine and 3753 received placebo or a basic analgesic alone.

The mean age for participants who received ketamine was 48 years, and 49 years for those who received control treatment. The distribution between men and women was equal. Types of surgery included ear, nose or throat surgery, wisdom tooth extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, knee joint replacement surgery, anterior cruciate ligament repair of the knee, knee arthroscopy, mastectomy, haemorrhoidectomy, abdominal surgery (laparotomy and lumbotomy), thyroid surgery, elective caesarean section and laparoscopic surgery.

Perioperative intravenous ketamine was compared with placebo in a large number of randomised studies and participants. Perioperative intravenous ketamine administration resulted in 19% reduction in postoperative opioid consumption both at 24 hours and 48 hours. Pain scores decreased by 19% at rest and by 22% during movement at 24 hours after surgery. At 48 hours, pain score reductions were 14% at rest and 16% on movement.

These results were, within the bounds of available data, consistent when analysed by subgroups of operation type or timing of administration, and sensitivity to study size and initial pain intensity.

The doses of ketamine used in the studies were broadly similar, precluding any sensible assessment of the effects of ketamine dose. Most studies using racemic ketamine administered 0.25 mg/kg or less. Pre-incisional doses of S-ketamine were typically 0.5 mg/kg. Infusion rates were similar for racemic and S-ketamine.

Perioperative intravenous ketamine reduced postoperative opioid consumption over 24 hours by almost 8 mg morphine equivalents (19% from 42 mg consumed by participants given placebo, moderate-quality evidence). Over 48 hours, opioid consumption was almost 13 mg lower (19% from 67 mg with placebo, moderate-quality evidence).

Perioperative intravenous ketamine also reduced pain at rest at 24 hours (5/100 mm lower, 19% lower from 26/100 mm with placebo, high-quality evidence), and 48 hours (5/100 mm, 22% lower from 23/100 mm, high-quality evidence). Pain during movement was also reduced at 24 hours (6/100 mm, 14% lower from 42/100 mm, moderate-quality evidence), and 48 hours (6/100 mm, 15% lower from 37 mm, low-quality evidence). A clinically important difference in pain is generally regarded as being around a 30% pain reduction (Farrar 2000, though that is determined in people with moderate or severe pain. Here, the mean pain scores are below 30/100 mm at 24 hours and 40/100 mm or below at 48 hours, which is at the limits of the inclusion criterion of 40/100 mm for moderate pain for many clinical trials. In arthritis, for instance, mean pain changes of 7 mm to 15 mm are seen for our most effective analgesics (Moore 2010). People in pain regard mild pain (typically below 30/100 mm) as an acceptable outcome when their pain is moderate or severe (Moore 2013). The goal of perioperative interventions is to avoid postoperative pain, and that generally means using a range of concomitant interventions to prevent it. People with postoperative pain scores below about 30/100 consider their experience is 'very good or excellent' (Mhuircheartaigh 2009). In that circumstance, it can be argued that ketamine effects are probably clinically relevant.

There was some evidence that ketamine was more efficacious in sensitivity analyses when pain scores were higher than 40/100 mm with control, that is, when pain was moderate or severe. Clinically, it is evident that if a certain patient group has little pain overall, it is not desirable to use an additional analgesic, such as ketamine, to the treatment regime. Summary table C demonstrates the difficulty in being able to make any definitive statement on the effect of higher pain scores. Numerically there was a larger effect on pain scores at rest and on movement at 24 and 48 hours. Where the high-pain-score trials were only a small part of the total, the size was large, but where these predominated, it was small (as for pain during movement at 24 hours). In the former case, the amounts of data are small, so that confidence intervals are wide. So the effects of ketamine may be larger at higher pain scores, but we cannot be sure.

Summary table C: effect of ketamine on VAS - all studies versus high pain score

Analysis	Studies	Participants	Participants (% of total)	VAS 0-100 (mm)
Pain at rest at 24 hours				
All studies	82	5004	100	−5 (−6.6 to −3.6)
Pain in control ≥ 40/100 mm	14	860	17	−17 (−25 to −9)
Pain during movement at 24 hours				
All studies	29	1806	100	−6 (−11 to −0.5)
Pain in control ≥ 40/100 mm	19	1300	72	−7 (−14 to −0.1)
Pain at rest at 48 hours				
All studies	49	2962	100	−5 (−6.7 to −3.4)
Pain in control ≥ 40/100 mm	6	259	12	−10 (−19 to −1.1
Pain during movement at 48 hours				
All studies	23	1353	100	−6 (−10 to −1.3)
Pain in control ≥ 40/100 mm	8	379	28	−10 (−14 to −6.1)

It has been suggested that concurrent administration of another NMDA-antagonist, nitrous oxide, could reduce the analgesic effect of ketamine when used as a component of general anaesthesia. We found no evidence of a reduced effect with ketamine and nitrous oxide as a component of general anaesthesia, with results very similar to those of the overall analysis.

Ketamine increased the time for the first postoperative analgesic request, by a mean of 54 minutes from 39 minutes with placebo. Despite a single study reporting an extraordinary increase of over 1000 minutes, its omission still provided evidence of a difference with an increase of 22 minutes.

Only seven studies with 333 participants investigated ketamine's effect on postoperative hyperalgesia, even though Bell 2006 pointed out the need for further research on this topic more than 10 years ago. The methods used for evaluating hyperalgesia in individual studies varied from asking the participants about an abnormal sensation on the wound to objective assessment of mechanical allodynia or hyperalgesia with von Frey filaments and mapping of these hyperalgesia areas around the surgical wound. Additionally, the time period for the assessment of hyperalgesia and presentation of the results were heterogeneous, thus limiting the eligibility of the data for quantitative analysis. In this review, ketamine was found to reduce postoperative hyperalgesia, though we recognise that the number of studies contributing to this outcome was small. The study methods were heterogeneous, contributing to the low-quality of evidence, and we were unable to draw any conclusions.

The occurrence of CNS adverse events was not significantly different in participants receiving ketamine (high-quality evidence). The included studies observed CNS adverse events in 187 participants (5%), receiving ketamine compared to 122 participants (4%), receiving control treatment. Results were no different in studies using benzodiazepine premedication (high-quality evidence). We were unable to include a large (672 participants), recent, study of the effects of ketamine on postoperative delirium because anaesthetic techniques were not standardised (Avidan 2017). Delirium was the primary outcome, and the study showed no difference between ketamine given in 0.5 mg/kg and 1.0 mg/kg bolus doses and placebo (19% for ketamine and placebo).

We found ketamine treatment reduced postoperative nausea and vomiting from 27% with placebo to 23% with ketamine; the NNTB to prevent one episode of postoperative nausea and vomiting with perioperative intravenous ketamine administration was 24 (95% CI 16 to 54; high-quality evidence). However, the effect size was smaller than previously reported (Bell 2006; Laskowski 2011).

Overall completeness and applicability of evidence

Based on large number of studies and consistency of response when results were subjected to subgroup and sensitivity analyses, we conclude that there is a general applicability of the evidence regarding intravenous perioperative ketamine. There are some limitations, discussed below, but the main clinical point will be how to use the evidence as part of multimodal anaesthetic techniques to improve postoperative outcomes and patient experience.

A positive bias in favour of a therapy might be found where there are small numbers of small studies (Dechartes 2013; Dechartres

2014; Fanelli 2017; Nguyen 2017; Nüesch 2010), even by the random play of chance (Brok 2009; Moore 1998; Thorlund 2011). Overemphasising results of underpowered studies or analyses has been criticised (AlBalawi 2013; Roberts 2015; Turner 2013). This review included a large number of small studies, which was probably the source of a high degree of heterogeneity in many analyses (Gavaghan 2000; Sterne 2000).

Small size was the major source of potential bias that might limit both the completeness and the applicability of any results. In the event, examining results in studies of group size larger than the median (30 participants per treatment arm), and performing analyses after eliminating studies at high risk of small size bias (fewer than 50 participants per treatment arm), generally supported the overall results, though data were occasionally limited. This provided confidence in the overall results.

Pain intensity varied between studies from very low pain scores with placebo equivalent to no or only mild pain, to scores indicating moderate or severe pain. The measurement of analgesic effect is accepted to be possible only when pain is present (McQuay 2012). We therefore examined results according to pain scores with placebo, and obtained similar or better analgesic effects with ketamine in studies where pain with placebo was moderate or severe. This also provided confidence in the overall results.

We recognise that the mean analgesic consumption as a measure for assessing analgesic efficacy of an intervention has been criticised because the distribution of analgesic consumption is not Gaussian but highly skewed, where a small number of participants consume over 50% of the analgesics in a study (Moore 2011). But the mean analgesic consumption as an outcome measure for analgesic efficacy is commonly used and reported in clinical studies, and is the only metric available. Opioids are associated with a large number of adverse events when used during surgery (Macintyre 2010).

We also recognise that pooling data from all operation types might weaken the overall applicability of the evidence. A series of subgroup analyses therefore explored the effects of ketamine by operation type (Appendix 4; Appendix 5). These results generally supported the overall results, although they were limited by small numbers in some cases. We were not able to conduct sensitivity analyses of each operation type due to the small number of participants.

We derived the available evidence on adverse events from a large population with an adequate number of CNS and emetic events, which allowed us to draw conclusions (Moore 1998). There was inadequate evidence to be conclusive about hyperalgesia, though there was an indication that ketamine may reduce postoperative hyperalgesia.

Quality of the evidence

We judged the risk of bias to be generally low, with few exceptions that failed to present all specified outcomes or presented results that had not been predefined, evoking suspicions of selective reporting. Although there was a large number of studies, many were small in size, with group sizes below 50 participants and thus at potential for high risk of bias. We demonstrated through sensitivity analysis that no size-related bias was apparent.

Our overall judgement of outcome quality was moderate. There were many studies and participants in many analyses; where we were able to demonstrate an absence of any small-study effect, we did not downgrade the evidence, but if that was not possible because of an insufficiency of larger studies, we downgraded because of potential small-study bias.

For adverse events, we typically judged this outcome to be high quality because of a consistent effect found over a large body of data.

Potential biases in the review process

We are not aware of any biases during the review process. The review authors (ECVB and ET), worked independently and agreed 'Risk of bias' assessments of individual studies, occasionally deferring to a third review author (VKK), when discrepancies arose. The review authors RAM, ECVB, and VKK assessed and agreed GRADE quality of the evidence.

Agreements and disagreements with other studies or reviews

Schmid 1999 stated that the intravenous administration route was effective in reducing postoperative pain intensity, supporting the findings of this review. However, we excluded from our review seven of the trials that investigated intravenous ketamine that they had included in their review because they did not meet our inclusion criteria (Clausen 1975; Edwards 1993; Jahangir 1993; Joachimmson 1986; Maurset 1989; Owen 1987; Wilder-Smith 1998).

The review by Subramaniam 2004 examined epidural and intravenous ketamine as an adjuvant analgesic to opioids. An analysis of 28 studies with intravenous ketamine administration found that adjuvant ketamine reduces postoperative pain intensity at 24 hours. Subramaniam 2004 supports the findings of this review. Additionally, the prevalence of CNS adverse events (9% with ketamine and 5% among control group), and postoperative nausea and vomiting (18% with ketamine and 27% among control participants), were comparable to our findings.

Elia and Tramér (Elia 2005), published their review in 2005 and their findings concerning the effect of pre-incisionally administered ketamine on cumulative morphine consumption at 24 hours (weighted mean difference −16 mg in favour of ketamine), are similar to our findings and support the findings of this review. Furthermore, the RR for nausea and vomiting in our review is equivalent to that found by Elia and Tramér (RR 0.89, 95% CI 0.52 to 1.51).

Based on the data from 37 trials, Bell 2006 concluded that perioperative ketamine reduced pain intensity, rescue analgesic requirements and postoperative nausea and vomiting. Bell 2006 included trials with epidural, intramuscular and intravenous administration routes. The findings of Bell 2006 support the findings of this review.

Laskowski 2011 observed beneficial effects of intravenous ketamine for postoperative analgesia in procedures involving the upper abdomen and thorax (i.e. especially painful procedures). Our findings are similar to this. Ketamine also reduced the incidence of postoperative nausea and vomiting. The findings of Laskowski 2011 support the findings of this review. In contrast to Laskowski's

findings, we did not observe a higher incidence of CNS adverse events with ketamine use.

Heesen 2014 found that intravenous ketamine during general anaesthesia did not delay the time to first request for opioid or reduce the total dose of postoperative opioid consumption. This does not support the findings of our review. However, Heesen 2014 focused on one study population (patients undergoing caesarean section), which may explain the discrepancy with our result.

AUTHORS' CONCLUSIONS

Implications for practice

For people with acute postoperative pain

Perioperative intravenous ketamine reduces postoperative opioid consumption and pain intensity, especially after thoracic surgery, major orthopaedic surgery and major abdominal surgery. In a non-stratified study population, perioperative intravenous ketamine administration reduces postoperative pain and opioid consumption to a lesser extent. Traditionally, 30% reduction in pain intensity and opioid consumption has been considered meaningful. However, even a smaller reduction in opioid consumption may be beneficial to those who are vulnerable to opioid-induced adverse events, for example, elderly people or those susceptible to postoperative nausea and vomiting, as well as individuals with opioid dependency. In a non-stratified study population, perioperative intravenous ketamine delays time to first request for analgesia. Ketamine may also reduce postoperative hyperalgesia, though more data are needed to support this preliminary result. Perioperative intravenous ketamine does not increase the risk of central nervous system (CNS) adverse events. The risk for postoperative nausea and vomiting is reduced.

For clinicians

Perioperative intravenous ketamine is beneficial for individuals undergoing thoracic, major orthopaedic, or major abdominal surgery. It may be more effective in situations with a higher background level of pain. Ketamine reduces postoperative opioid consumption and the risk for postoperative nausea and vomiting and may therefore be beneficial for individuals who are vulnerable to opioid-induced adverse events, for example, the elderly, those susceptible to postoperative nausea and vomiting, as well as individuals with opioid tolerance or dependency. Ketamine may also reduce postoperative hyperalgesia, but more data are needed to support this finding.

For policy makers

Perioperative intravenous ketamine should be targeted to those who are likely to benefit from ketamine's analgesic and opioid-sparing effect.

For funders

The amount and quality of evidence around the benefits and harms of perioperative intravenous ketamine is moderate or high. The results are buttressed by several subgroup and sensitivity analyses that support the main findings. These include type of surgery, co-administration with nitrous oxide or use of benzodiazepine premedicant, timing of use, and level of pain intensity with controls. There is no evidence that perioperative intravenous ketamine increased the risk of CNS adverse events.

Implications for research

General implications

This review of intravenous perioperative ketamine revealed no major problems with the evidence available, other than the generally small size of studies. While this pattern has not been uncommon in anaesthetic research, there is growing evidence that small study size is associated with potential major biases. These are such as to raise ethical as well as scientific considerations for future studies of similar size. This might mean reconsideration of how studies are performed in future. Perhaps multicentre, randomised, controlled study design with more than 200 participants per treatment arm, compared to randomised studies with fewer than 50 participants per treatment arm, would increase confidence in any findings.

Design

Many of the studies in this review had low pain intensity with controls. That is good, because low pain intensity is valued by people in pain, including postoperatively (Mhuircheartaigh 2009; Moore 2013). The value of pain intensity reduction is probably more highly regarded by people with moderate or severe pain than with those with moderate or no pain. For future studies, it may be more informative to explore multimodal anaesthesia with intravenous ketamine with one component in situations with higher levels of pain.

Measurement (endpoints)

Mean opioid consumption has been shown to be highly skewed, and probably meaningless (Moore 2011). Future studies might usefully concentrate on reporting the number of people with high opioid consumption. Relevant endpoints could also include patient-reported outcome measures for postoperative recovery, for example, patient satisfaction.

Other

Future studies should assess the effect of ketamine's different timing and dosing regimens on postoperative pain, opioid consumption and adverse events. Additionally, subgroups who may benefit from ketamine's analgesic and opioid-sparing effect warrant more research. These subgroups are, for example, the elderly and other individuals who are sensitive to adverse events that often accompany opioid medication. So far, the data on ketamine's effect on individuals with a history of substance abuse are limited. Additionally, determining whether specific study populations are more susceptible to ketamine-related adverse events, as well as clarifying ketamine's role in prevention of persistent postsurgical pain among patients with a high risk of chronic pain, would also be of clinical interest. Ketamine's antihyperalgesic effect also warrants more research because so far the data are sparse. Studies examining the effect of ketamine as adjuvant to specific opioids would also be of interest, since recent animal data suggest that ketamine and morphine have beneficial interactions (Lilius 2015).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdolahi 2013

Study characteristics		
Methods	Randomised, placebo control	
Participants	N = 88, about 41% women	
Interventions	Ketamine 0.5 mg/kg bolus IV during induction of anaesthesia	
Outcomes	Pain intensity (VAS). Analgesic consumption. Pain outcomes reported during the recovery room stay. PONV	
Surgery type	Ophthalmic surgery (retinal detachment, strabismus, keratoplasty)	
Group numbers after end of study (treatment/control)	44/44	
Age of patient population (treatment/control)	35 ± 13.4 36.3 ± 17.8	
Notes	No funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded investigator not participating in patient care performed data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	44 participants per treatment arm

Adam 2005

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40, about 68% women
Interventions	Ketamine 0.5 mg/kg bolus IV just after the induction of anaesthesia followed by a continuous infusion of 3 µg/kg/min intraoperatively and then 1.5 µg/kg/min for 48 h postoperatively
Outcomes	Pain intensity (VAS) before and after mobilisation. PCA morphine consumption. Main outcomes reported hourly for 4 h, then every 4 h for 48 h. Time to first analgesic request. AEs
Surgery type	Total knee arthroplasty
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	68 ± 8 69 ± 6
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number table was generated
Allocation concealment (selection bias)	Low risk	Allocation concealed in sealed and sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel; a nurse not involved in the evaluation of the participants prepared study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel; none of the other investigators involved in participant management and data collection was aware of the group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	High risk	No data available of all predefined AEs
Size	High risk	20 participants per treatment arm

Adriaenssens 1999

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 30, about 77% women
Interventions	Ketamine IV infusion initially 10 µg/kg/min, gradually decreased to 2.5 µg/kg/min for 48 h after surgery
Outcomes	Pain intensity (VAS). PCA morphine consumption. AEs. Outcomes reported at 0, 1, 2, 4, 6, 12, 24, 36 and 48 h after surgery
Surgery type	Laparotomy
Group numbers after end of study (treatment/control)	15/15
Age of patient population (treatment/control)	Mean values (range) 53 (27-83) 51 (17-82)
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described, only mentioned "patients were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Said to be double-blind but blinding process not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes reported
Size	High risk	15 participants per treatment arm

Aida 2000

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 121, of whom 60 participants in groups 2 and 4 (IV ketamine and control). 40% women
Interventions	1. Ketamine 1 mg/kg IV prior to surgical incision, 0.5 mg/kg/h infusion IV until skin closure 2. Morphine ED bolus prior to surgical incision + infusion + placebo IV bolus + continuous infusion until skin closure 3. Placebo ED + ketamine IV bolus 1 mg/kg + infusion 0.5 mg/kg/h 4. Morphine ED + ketamine IV
Outcomes	Pain intensity (VAS). Maximum 48 h pain (categorical scale). PCA morphine consumption. Outcomes reported at 6, 12, 24 and 48 h
Surgery type	Distal or total gastrectomy
Group numbers after end of study (treatment/control)	29/31
Age of patient population (treatment/control)	62 ± 14 63 ± 13
Notes	Support from institutional and/or departmental sources

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "According to a computer-generated table of random number assignments, each patient was assigned to one of four groups."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study supervisor prepared the drug solutions, which were sealed in an envelope and transferred to the anesthesiologist blinded to the solutions."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes were reported
Size	High risk	29 and 31 participants per treatment arms, respectively

Aqil 2011

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 120, about 58% women
Interventions	1. Ketamine 0.5 mg/kg bolus IV at induction 2. Ketamine 1 mg/kg bolus IV 3. Ketamine 1.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS). Pain intensity results not reported though predefined in methods. Analgesic consumption (ketoprofen) at 24 h. AEs
Surgery type	Septorhinoplasty
Group numbers after end of study (treatment/control)	90/30
Age of patient population (treatment/control)	22.9 ± 4.5 22.3 ± 3.89
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel and identical study drug syringes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	VAS scores not reported but defined in methods. Time to first request for analgesia reported but not predefined
Size	High risk	30 participants per treatment arm

Argiriadou 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 45, 20% women
Interventions	1. S-ketamine 0.5 mg/kg bolus IV prior to surgical incision 2. Pre-incisional S-ketamine 0.5 mg/kg bolus IV + intraoperative 0.2 mg/kg boluses IV at 20-min intervals until skin closure
Outcomes	Pain intensity (VAS). Cumulative consumption of diclofenac and dextropropoxyphene. Outcomes recorded at 3, 6 and 24 h after awakening.
Surgery type	Major abdominal surgery
Group numbers after end of study (treatment/control)	30/15
Age of patient population (treatment/control)	61 ± 14 61 ± 10
Notes	Supported in part by Pfizer Parke-Davis Pharmaceuticals, Freiburg- Karlsruhe, Germany.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table. Quote: "With use of a computer-generated randomization table, patients were assigned to one of three groups."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and personnel who participated in the study were unaware of group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients and personnel who participated in the study were unaware of group assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	11% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	30 and 15 participants per treatment arm

Argiriadou 2011

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 80, 21% women
Interventions	Pre-incisional S-ketamine 0.5 mg/kg bolus IV + intraoperative infusion 6.7µg/kg/min until 20 min before the end of surgery
Outcomes	Pain intensity (VAS) at 4, 12, 24 and 48 h after surgery at rest and during movement (coughing). Supplemental analgesic requirement. Pulmonary function. Return of bowel functions. Length of ICU and hospital stay
Surgery type	Elective open thoracotomy
Group numbers after end of study (treatment/control)	27/26
Age of patient population (treatment/control)	52 ± 17 59 ± 11
Notes	No funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	High risk	26, 27 and 27 participants per treatment arm

Arikan 2016

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 120, of whom 80 participants in IV ketamine and control treatment arms. 100% women
Interventions	Postoperatively: 1. ketamine 0.2 mg/kg IV bolus followed by an infusion of ketamine 0.05 mg/kg/h for 48 h 2. 0.9% saline bolus IV followed by an infusion of 0.9% saline for 48 h 3. (IV bolus of magnesium 50 mg/kg followed by an infusion of magnesium 10 mg/kg/h)
Outcomes	48 h cumulative morphine consumption. Pain intensity (NPRS) reported at 2, 6, 12, 24 and 48 h postoperatively. AEs
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	40/40
Age of patient population (treatment/control)	59.35 ± 4.96 58.46 ± 5.71
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	40 participants per treatment arm

Ataskhoyi 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 100% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS) reported at 1, 2, 3, 6, 12 and 24 h postoperatively. Time to first request for analgesia. Analgesic consumption reported at 24 h. AEs
Surgery type	Diagnostic gynaecological laparoscopy
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	32.7 ± 3.4 34.3 ± 5.4
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Aubrun 2008

Study characteristics

Aubrun 2008 *(Continued)*

Methods	Randomised, double-blind, placebo control
Participants	N = 90, 100% women
Interventions	Pre-incisional ketamine 0.15 mg/kg bolus IV + IV PCA ketamine 0.5 mg/bolus
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Outcomes reported every 6 h up to 48 h
Surgery type	Major gynaecological operation
Group numbers after end of study (treatment/control)	45/45
Age of patient population (treatment/control)	50 ± 10 49 ± 12
Notes	Support provided by departmental sources

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	12% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	45 participants per treatment arm

Aveline 2006

Study characteristics

Methods	Randomised, double-blind, ketamine vs ketamine + morphine vs morphine
Participants	N = 69, of whom 45 participants in IV ketamine and control arms. About 50% women

Aveline 2006 *(Continued)*

Interventions	Pre-incisional bolus of ketamine 0.15 mg/kg + morphine 0.1 mg/kg IV
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Outcomes reported every 4 h up to 24 h
Surgery type	Elective surgical lumbar discectomy with partial laminectomy and nucleotomy
Group numbers after end of study (treatment/control)	45/23
Age of patient population (treatment/control)	46.6 ± 10.6 44.4 ± 11.2
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22, 23 and 23 participants per treatment arm

Aveline 2009

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 75, of whom 49 participants in IV ketamine and control arms. About 61% women
Interventions	Pre-incisional ketamine 0.2 mg/kg bolus IV + continuous IV infusion 120 µg/kg/h until the end of surgery, then 60 µg/kg/h until the second postoperative day

Aveline 2009 *(Continued)*

Outcomes	Pain intensity (VAS). Analgesic consumption. Time to first morphine demand, AEs. Pain outcomes reported at 2, 6, 12 24 and 48 h
Surgery type	Elective unilateral total knee replacement
Group numbers after end of study (treatment/control)	25/24
Age of patient population (treatment/control)	71 ± 9 70 ± 7
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Sequence allocation concealed by opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25, 24 and 25 participants per treatment arm

Ayoglu 2005

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 60, of whom 40 participants in IV ketamine and control treatment arms. 65% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + infusion 0.15 mg/kg/h for the next 4 h
Outcomes	Pain intensity (VRS, NRS). PCA morphine requirement. Pain outcomes reported hourly up to 4 h postoperatively, then at 8 and 20 h postoperatively. AEs

Ayoglu 2005 *(Continued)*

Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	52.9 ± 9 49.1 ± 3.7
Notes	Third group received a bolus and infusion of magnesium sulphate. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation done by using coloured balls
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Unpleasant dreams not predefined in 'methods' but reported in 'results'
Size	High risk	20 participants per treatment arm. Lacks power analysis

Barreveld 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 59, 56% women
Interventions	Postoperative ketamine 0.2 mg/kg/h infusion IV for 24 h
Outcomes	Pain intensity (NRS for categorical pain states). Analgesic consumption at 24 h. AEs
Surgery type	Nononcologic surgery leading to hospitalisation

Barreveld 2013 *(Continued)*

Group numbers after end of study (treatment/control)	29/30
Age of patient population (treatment/control)	48.5 ± 11.9 55 ± 11.2
Notes	Intraoperative anaesthetic management was at the discretion of the attending anaesthetist (not standardised). No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail
Allocation concealment (selection bias)	Low risk	Central allocation by Investigational Drug Service (IDS (a third party)). IDS also prepared study solutions that were identical in appearance and labelled as "ketamine/placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	29 and 30 participants per treatment arm

Bilgen 2012

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 140, 100% women
Interventions	Before induction of anaesthesia 1. Ketamine 0.25 mg/kg 2. Ketamine 0.5 mg/kg 3. Ketamine 1 mg/kg bolus IV

Bilgen 2012 *(Continued)*

Outcomes	Pain intensity (NRS). Analgesic consumption. Outcomes reported at 2, 6, 12, 18, 24, 48 h and 2 weeks, 1 and 6 months and 1 year postoperatively
Surgery type	Caesarean section
Group numbers after end of study (treatment/control)	105/35
Age of patient population (treatment/control)	31 ± 4 32 ± 4
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Outcomes that are not defined in "methods" are reported
Size	High risk	35 participants per treatment arm

Bornemann-Cimenti 2016

Study characteristics

Methods	Randomised, triple-blind, placebo control
Participants	N = 60, about 52% women
Interventions	After induction of anaesthesia 1. 0.25 mg/kg IV bolus of S-ketamine followed by a 0.125 mg/kg/h infusion for 48 h 2. 0.9% IV saline bolus followed by a 0.015 mg/kg/h infusion of S-ketamine for 48 h

Bornemann-Cimenti 2016 *(Continued)*

	3. 0.9% saline bolus IV followed by a 0.9% saline infusion for 48 h
Outcomes	Postoperative opioid consumption, pain intensity (NRS), hyperalgesia at the incision site, delirium scores. Pain outcomes reported over time every 4 h up to 48 h. Hyperalgesia and ICDSC reported at 48 h
Surgery type	Major abdominal surgery
Group numbers after end of study (treatment/control)	37/19
Age of patient population (treatment/control)	60.2 ± 9 61 ± 12.4
Notes	Institutional funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only mentioned that an anaesthetist with no further involvement in the study prepared and labelled study drug syringes with "study medication" and the randomisation number of the participant
Blinding of participants and personnel (performance bias) All outcomes	Low risk	An independent anaesthesiologist prepared study drugs. Participants and nursing staff were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel made outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Burstal 2001

Study characteristics	
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 70, 100% women
Interventions	Postoperative PCA ketamine 2 mg/bolus IV

Burstal 2001 *(Continued)*

Outcomes	Pain intensity (VAS) and PCA morphine consumption reported at 24 and 48 h. Area of allodynia (von Frey) reported at 48 h
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	37/33 Allodynia subset: 25/18
Age of patient population (treatment/control)	Median values, IQR 43 (10) 45 (7) Allodynia subset: 45 (10), 44 (7)
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated groups
Allocation concealment (selection bias)	Low risk	Quote: "A sealed envelope system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	16% was withdrawn
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes reported but surgeon or participant decided on PCA cessation based on how they felt
Size	High risk	37 and 33 participants per treatment arm

Cenzig 2014

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N= 60, about 73% women
Interventions	Intraoperative ketamine infusion 6 µg/kg/min after orotracheal intubation until wound closure

Cenzig 2014 *(Continued)*

Outcomes	Pain intensity (VAS) and analgesic consumption, reported at 1, 3, 6, 12 and 24 h. Time to first analgesic request. AEs during the first 24 h
Surgery type	Total knee replacement surgery
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	58.2 ± 9.58 58.8 ± 11.5
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses unaware of the study protocol performed assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	30 participants per treatment arm

Chazan 2010

Study characteristics

Methods	Randomised, double-blind
Participants	N = 46, about 35% women
Interventions	Postoperative ketamine 5 mg + morphine 1 mg/bolus IV via PCA vs morphine alone
Outcomes	Pain intensity (VAS) reported at 24 and 48 h. Analgesic consumption reported at 72 h. AEs.

Chazan 2010 *(Continued)*

Surgery type	Minimally invasive direct coronary artery bypass, off-pump coronary artery bypass, thoracotomy
Group numbers after end of study (treatment/control)	24/22
Age of patient population (treatment/control)	60 ± 16 57 ± 18
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence of the patients was generated and concealed at the computer"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel and participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22 and 24 participants per treatment arm

Chen 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40. Demographic data of study participants not presented
Interventions	Pre-incisional ketamine 0.3 mg/kg bolus IV followed by an infusion 3 µg/kg/min until 15 mins prior to completion of the operation
Outcomes	Pain intensity (VAS). Analgesic consumption. Pain outcomes reported at 3, 6, 12, 24 and 48 h postoperatively. Psychotomimetic AEs
Surgery type	Upper abdominal surgery

Chen 2004 *(Continued)*

Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	Not mentioned
Notes	Article in Chinese. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only mentioned "randomised"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	High risk	Not all predefined outcomes reported
Size	High risk	20 participants per treatment arm

Choi 2015

Study characteristics	
Methods	Randomised, double-blind
Participants	N = 75, 100% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV followed by an infusion 5 µg/kg/min
Outcomes	Analgesic consumption reported at 48 h postoperatively. Pain intensity (NRS) reported at 0, 1, 6 and 24 h postoperatively. Time to first analgesic demand. Hyperalgesia (sensory threshold)
Surgery type	Laparoscopic gynaecologic surgery
Group numbers after end of study (treatment/control)	25/25

Choi 2015 *(Continued)*

Age of patient population (treatment/control)	44.4 ± 9.2 43.7 ± 7.6
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only mentioned "randomised"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Colombani 2008

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 208, 100% women
Interventions	Pre-incisional ketamine 0.15 mg/kg bolus IV followed by an infusion 2 µg/kg/min until the end of surgery
Outcomes	Analgesic consumption reported at 48 h postoperatively. Pain intensity (VAS), reported as participant proportion with VAS score > 4
Surgery type	Breast surgery (partial resection of breast with axillary lymph node evacuation or mastectomy with or without axillary lymph node evacuation)
Group numbers after end of study (treatment/control)	106/102

Colombani 2008 *(Continued)*

Age of patient population (treatment/control)	57.6 ± 12.5 59 ± 11.4
Notes	Article in French. Only participant proportion (%) with VAS score > 4 reported. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated at the department of biostatistics
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	Unclear risk	106 and 102 participants per treatment arm

Crousier 2008

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 36, 100% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV followed by an infusion 0.25 mg/kg/h until wound closure
Outcomes	Pain intensity (VAS) and analgesic consumption reported at 24 h. AEs. Hyperalgesia on 5th postoperative day and after 3 months
Surgery type	Mastectomy
Group numbers after end of study (treatment/control)	18/18
Age of patient population (treatment/control)	60 ± 11

Crousier 2008 *(Continued)*

	49 ± 12
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only mentioned double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	High risk	Pain score measures at certain time points predefined in methods but only average pain scores in the postoperative period reported
Size	High risk	18 participants per treatment arm

D'Alonzo 2011

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 40, about 43% women
Interventions	Ketamine 0.5 mg/kg bolus IV prior to chest wall incision
Outcomes	Pain intensity (NRS). Reported at baseline, 4 and 24 h postoperatively
Surgery type	Video assisted thoracoscopic surgery or thoracotomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	61 ± 12 66 ± 10
Notes	Inflammatory response as a primary outcome of the study. No mention of sponsorship or funding

D'Alonzo 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes reported but the anaesthetic procedure was left to the discretion of the anaesthesiologist; general anaesthesia was supplemented by an epidural catheter placement as needed to control pain (16 participants in the treatment group, 19 participants in the control group)
Size	High risk	20 participants per treatment arm

Dahi-Taleghani 2014

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 140, 100% men
Interventions	Postoperative ketamine 2 mg + morphine 2 mg via PCA
Outcomes	Pain intensity (VAS) reported at 1, 6 and 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Elective orthopedic surgery for the lower limb
Group numbers after end of study (treatment/control)	70/70
Age of patient population (treatment/control)	39.1 ± 7.2 38.3 ± 7.5
Notes	The study was supported financially in part by a research grant from the Anesthesiology Research Center, Shadid Beheshti University of Medical Sciences, Tehran, Iran

Dahi-Taleghani 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only mentioned double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	Unclear risk	70 participants per treatment arm

Dahl 2000

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 89, 100% women
Interventions	1. Ketamine bolus 0.4 mg/kg IV prior to skin incision 2. Ketamine bolus 0.4 mg/kg IV at skin closure
Outcomes	Pain intensity (VAS, VRS) reported every 1 h up to 6 h postoperatively, then 6-24 and 24-96 h. Analgesic consumption at 0-6, 6-24 and 24-48 h postoperatively. Level of activity. AEs
Surgery type	Abdominal hysterectomy
Group numbers after end of study (treatment/control)	60/29
Age of patient population (treatment/control)	50.1 ± 5.3 48 ± 7
Notes	No mention of sponsorship or funding
Risk of bias	

Dahl 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding process not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding process not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	10% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	33 and 27 participants per treatment arm and 29 participants in the control group

Dal 2005

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 90, of whom 60 participants in IV ketamine and control treatment arms. 78% women
Interventions	Ketamine 0.5 mg/kg bolus IV 20 mins before the end of surgery
Outcomes	Postoperative shivering. Pain intensity (VAS) reported on arrival in the recovery room and at 1st and 2nd h postoperatively. Time to first analgesic requirement. AEs
Surgery type	Various procedures. General anaesthesia for an anticipated duration of 60-180 mins excluding procedures that might require administration of blood or blood products and urological endoscopic operations
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	45 (21-66) 43 (18-65)
Notes	Main outcome was postoperative shivering. No mention of sponsorship or funding
Risk of bias	

Dal 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	30 participants per treatment arm

Dar 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 90, of whom 60 participants in IV ketamine and control treatment arms. 30% women
Interventions	Ketamine 0.5 mg/kg bolus IV 20 mins before the end of surgery. Various surgical procedures
Outcomes	Postoperative shivering, pain intensity (VAS), AEs, vital parameters. Pain intensity not reported
Surgery type	Various procedures under general anaesthesia with an anticipated duration of 60-180 mins excluding urological endoscopic operations
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	36.63 ± 1.2 38.7 ± 1.7
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Dar 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail
Allocation concealment (selection bias)	Low risk	Quote: "Study drugs were prepared, diluted to a volume of 5 ml and presented as coded syringes by an anaesthetist who was not involved in the management of the patients"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A blinded anaesthetist made assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Predefined VAS scores are not reported. Mean time to rescue analgesia is reported even though not predefined in methods.
Size	High risk	30 participants per treatment arm

De Kock 2001

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 100, of whom 60 participants in IV ketamine or control treatment arms. About 48% women
Interventions	1. ± 30 min before skin incision: ketamine bolus 0.25 mg/kg IV + infusion 0.125 mg/kg/h until end of surgery 2. ± 30 min before skin incision: ketamine bolus 0.5 mg/kg IV + infusion 0.25 mg/kg/h IV until skin closure 3. Ketamine 0.25 mg/kg bolus ED + infusion 0.125 mg/kg/h ED until end of surgery 4. Ketamine 0.5 mg/kg bolus ED + infusion 0.25 mg/kg/h ED until end of surgery
Outcomes	Pain intensity (VAS) reported at 15 min, 2, 6, 12, 24, 36 and 48 h postoperatively. Area of hyperalgesia reported at 24, 48 and 72 h postoperatively. Postoperative residual pain at 2 weeks, 1 and 6 months, 1 year. Cumulative number of met and unmet PCA morphine demands. AEs
Surgery type	Rectal adenocarcinoma surgery
Group numbers after end of study (treatment/control)	40/20
Age of patient population (treatment/control)	67 ± 8.4 67 ± 9
Notes	No mention of sponsorship or funding

De Kock 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals in the immediate postoperative period. 8% of participants died during the one-year follow up
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Deng 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 200, about 43% women
Interventions	1. Pre-incisional ketamine 0.5 mg/kg bolus IV + 0.1 mg/kg/h infusion IV during surgery and for 24 h postoperatively 2. Pre-incisional ketamine 0.5 mg/kg bolus IV + 0.05 mg/kg/h infusion IV during surgery and for 24 h postoperatively 3. Pre-incisional ketamine 0.5 mg/kg bolus IV + 0.01 mg/kg/h infusion IV during surgery and for 24 h postoperatively
Outcomes	Pain intensity (VAS) reported at 24 h postoperatively. PCA remifentanil consumption, reported at 0-12 h, 12-24 h and 0-24 h postoperatively. AEs. Participant satisfaction with analgesia
Surgery type	Lower limb fracture operation
Group numbers after end of study (treatment/control)	150/50
Age of patient population (treatment/control)	49.6 ± 5.6 50.1 ± 6.3

Deng 2009 *(Continued)*

Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	Low risk	Predefined outcomes addressed
Size	Unclear risk	50 participants per treatment arm

Du 2011

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 40, 100% women
Interventions	Preinductional ketamine 0.25 mg/kg bolus IV
Outcomes	Pain intensity (VAS) and analgesic consumption reported at 15 min intervals during the first postoperative hour. AEs
Surgery type	Gynaecological laparoscopic surgery
Group numbers after end of study (treatment/control)	20/20. Power analysis calculated based on the primary outcome (serum glucose level)
Age of patient population (treatment/control)	35.4 ± 7.9 39.1 ± 11.5
Notes	Main outcome was endocrine metabolic and inflammatory responses to preoperative low-dose ketamine. No mention of sponsorship or funding

Du 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Dualé 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 86, about 30% women
Interventions	Ketamine 1 mg/kg bolus IV at induction + 1 mg/kg/h infusion IV
Outcomes	Pain intensity (VAS) reported on arrival in the PACU and 1, 2, 4, 8, 12, 16, 24, 62, 40 and 48 h postoperatively. Analgesic consumption reported at 24 and 48 h postoperatively. AEs. NPSI scores reported at 6 weeks and 4 months postoperatively
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	42/44
Age of patient population (treatment/control)	61.9 ± 8.3 58.5 ± 8.5
Notes	No financial arrangements that may represent a conflict of interest
Risk of bias	

Dualé 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail
Allocation concealment (selection bias)	Low risk	Quote: "An inclusion number was allocated randomly and kept in a sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	42 and 44 participants per treatment arm

Dullenkopf 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 120; about 59% women
Interventions	1. Pre-incisional ketamine 0.15 mg/kg bolus IV 2. Pre-incisional ketamine 0.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS) at arrival in PACU and at 3 months postoperatively. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	General surgical or orthopaedic operation anticipated to last 30 to 90 mins and assumed hospital stay of 48 h
Group numbers after end of study (treatment/control)	77/33
Age of patient population (treatment/control)	52.6 ± 18 52.3 ± 17.9
Notes	Basis for group size unclear (power analysis not presented). No mention of sponsorship or funding
Risk of bias	

Dullenkopf 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Study solutions prepared and blinded by a hospital pharmacist (a third party). Syringes containing study drugs identical in appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	36, 41 and 33 participants per treatment arm

Fiorelli 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 75, 27% women
Interventions	Ketamine 1 mg/kg bolus IV before thoracotomy
Outcomes	Pain intensity (VAS) and morphine consumption reported at 6, 12, 24, 36 and 48 h postoperatively. AEs. Inflammatory response
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	38/37
Age of patient population (treatment/control)	59.5 ± 15.3 58.6 ± 17.4
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Fiorelli 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	High risk	38 and 37 participants per treatment arm

Galinski 2007

Study characteristics	
Methods	Randomised, double-blind. Ketamine + dexamethasone vs dexamethasone
Participants	N = 65, about 26% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS) and analgesic consumption, reported at 15 and 30 min postoperatively. AEs
Surgery type	Inguinal hernia repair
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	47.55 ± 17.46 49.6 ± 13.36
Notes	Support provided by institutional and/or departmental sources

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail

Galinski 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in detail, said to be double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Ganne 2005

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 61, about 7% women
Interventions	Ketamine 0.15 mg/kg bolus IV before induction of anaesthesia + 2 µg/kg/min infusion IV during anaesthesia
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Pain outcomes reported every 8 h up to 48 h postoperatively
Surgery type	Ear, throat and nose surgery
Group numbers after end of study (treatment/control)	30/31
Age of patient population (treatment/control)	56.9 ± 9.5 59.3 ± 8.9
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table

Ganne 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment in sealed envelopes. Syringes containing study drugs were identical in appearance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 and 31 participants per treatment arm

Garcia-Navia 2016

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 33, 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV prior to incision
Outcomes	Opioid consumption during surgery, emergence time, pain intensity (VAS) on admission to PACU and at 2, 4, 8 and 24 h postoperatively. Analgesic consumption at 24 h postoperatively. AEs
Surgery type	Gynecological laparotomy excluding oncologic surgery
Group numbers after end of study (treatment/control)	11/11
Age of patient population (treatment/control)	43.1 ± 7.2 45.2 ± 4.2
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described. Only mentioned that an independent nurse not involved in the study prepared study solutions

Garcia-Navia 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	11 participants per treatment arm

Garg 2016

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 66, about 63% women
Interventions	Postoperative administration of 1. ketamine bolus 0.25 mg/kg IV followed by a continuous infusion at a rate of 0.25 mg/kg/h for 24 h or 2. 0.9% saline bolus IV followed by a 0.9% saline infusion (or an IV bolus of dexmedetomidine 0.5µg/kg followed by an infusion at a rate of 0.3 µg/kg/h
Outcomes	Pain intensity (NRS) at 0, 2, 6, 12, 18, 24 and 48 h postoperatively. Pain-free period. Analgesic consumption at 12, 24 and 48 h postoperatively. AEs
Surgery type	Spine surgery
Group numbers after end of study (treatment/control)	22/22
Age of patient population (treatment/control)	36.45 ± 13.39 36.32 ± 14.32
Notes	Surgery types include laminectomy and excision, pedicle screw fixation, decompression and stabilisation, detethering and excision of tumour). No funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list

Garg 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment achieved by sequentially numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in detail. Only mentioned "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in detail. Only mentioned double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22 participants per treatment arm

Gilabert Morell 2002

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 69, 100% women
Interventions	1. Ketamine 0.15 mg/kg bolus IV at induction 2. Ketamine 0.15 mg/kg bolus IV at wound closure
Outcomes	Pain intensity (VAS) at rest at 1, 6, 24 and 48 h postoperatively and during movement on 1st and 5th day postoperatively. Time to first request of PCA. Morphine consumption at 6, 24 and 48 h postoperatively. AEs
Surgery type	Hystectomy and adenectomy
Group numbers after end of study (treatment/control)	44/22
Age of patient population (treatment/control)	47.8 ± 8.3 48 ± 7
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described

Gilabert Morell 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	High risk	23 participants per treatment arm

Grady 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control. Factorial design. No direct comparison between ketamine vs non-ketamine
Participants	N = 64, 100% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + a continuous infusion 0.12 mg/kg/h until 15 mins before completion of the operation
Outcomes	Pain intensity (VRS) reported on PACU admit and discharge and on 1st and 2nd postoperative days. Analgesic consumption reported in PACU and on 1st and 2nd postoperative days. AEs
Surgery type	Abdominal hysterectomy
Group numbers after end of study (treatment/control)	30/32
Age of patient population (treatment/control)	46 ± 8 46 ± 8
Notes	Internal funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation based on a computer-generated list

Grady 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation maintained in sequentially numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 and 32 participants per treatment arm.

Guignard 2002

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 50, 50% women
Interventions	Ketamine bolus 0.15 mg/kg + infusion 2 µg/kg/min IV from prior to skin incision until skin closure
Outcomes	Pain intensity (VAS and 4-point VRS; data not shown). Total morphine consumption (PCA and nurse-administered) at 0-4, 5-24 and 0-24 h postoperatively. Time to first request for morphine. AEs
Surgery type	Abdominal surgery
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	64 ± 10 61 ± 13
Notes	Supported, in part, by NIH Grant GM 58273 (Bethesda, MD), the Joseph Drown Foundation (Los Angeles, CA), and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random-number table

Guignard 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only mentioned that a hospital pharmacist prepared study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded person collecting data
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Guillou 2003

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 101, about 54% women
Interventions	Ketamine 0.5 mg/kg bolus IV after surgery + infusion 2 µg/kg/min for 24 h and 1 µg/kg/min from 24-48 h
Outcomes	Pain intensity (VAS) at rest and during movement. Cumulative dose of PCA morphine. Outcomes reported every 4 h up to 48 h postoperatively
Surgery type	Major abdominal surgery
Group numbers after end of study (treatment/control)	41/52
Age of patient population (treatment/control)	60 ± 16 60 ± 15
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described

Guillou 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observer
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	Unclear risk	41 and 52 participants per treatment arm

Hadi 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 30. Table of demographic data not presented
Interventions	Ketamine 1 µg/kg/min infusion IV until the end of surgery
Outcomes	Pain intensity (visual face-rating scale), reported as number of participants with different degrees of pain. Time to first request for analgesia. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Lumbar and thoracic spinal fusion surgery
Group numbers after end of study (treatment/control)	15/15
Age of patient population (treatment/control)	Age range 53-59 49-58
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not described

Hadi 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described, only mentioned double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data assessment by blinded pharmacy students
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	15 participants per treatment arm

Hadi 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 45, about 53% women
Interventions	1. Ketamine 1 µg/kg/min infusion IV intraoperatively 2. Ketamine 1 µg/kg/min infusion IV intraoperatively and 24 h after surgery
Outcomes	Pain intensity (VAS). Analgesic consumption. Pain outcomes reported at 6, 12 and 24 h postoperatively. Time to first request for analgesia. AEs
Surgery type	Lumbar microdiscectomy
Group numbers after end of study (treatment/control)	30/15
Age of patient population (treatment/control)	55 ± 2.5 51 ± 2.47
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described

Hadi 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacist prepared study solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel collecting data
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Pain intensity scale reported differs (VAS, NRS)
Size	High risk	15 participants per treatment arm

Haliloglu 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 52, 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV at induction followed by an infusion 10 mcg/kg/min until the end of surgery
Outcomes	Pain intensity (NRS) reported at 15 min, at 2 and 6 h, then every 6 h up to 24 h postoperatively. Analgesic consumption reported at 6-h intervals up to 24 h postoperatively. Cumulative analgesic consumption reported at 24 h postoperatively. Rescue analgesia. AEs
Surgery type	Elective caesarean section
Group numbers after end of study (treatment/control)	26/26
Age of patient population (treatment/control)	29.1 ± 2.2 29 ± 2.2
Notes	No mention of sponsorship or funding. The study authors report that they have no conflicts of interest

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table

Haliloglu 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	26 participants per treatment arm

Hasanein 2011

Study characteristics	
Methods	Randomised, blinded, placebo controlled
Participants	N = 60, about 47% women
Interventions	Ketamine 1 µg/kg/min infusion IV during anaesthesia
Outcomes	Pain intensity (VAS), reported at 1 and 2 h postoperatively. Time to first request for analgesia. Analgesic consumption, reported at 24 h postoperatively. AEs
Surgery type	Laparoscopic Roux-en-Y-gastric bypass
Group numbers after end of study (treatment/control)	30/30. Power analysis not provided
Age of patient population (treatment/control)	29 ± 6 27 ± 8
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No data provided

Hasanein 2011 *(Continued)*

Allocation concealment (selection bias)	High risk	The attending anaesthesiologist was aware of the treatment condition but study participants and personnel in the operating room and recording data were unaware of treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and investigators recording data in the operating room were blinded to the treatment but the attending anaesthesiologist was aware of the treatment condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators recording data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Predefined outcome (PCA morphine consumption during the first 4 h after surgery) is not reported
Size	High risk	30 participants per treatment arm

Hayes 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 45, about 42% women
Interventions	Pre-induction ketamine 0.5 mg/kg bolus IV followed by 0.15 mg/kg/h infusion IV for 72 h postoperatively
Outcomes	Incidence of post-amputation pain (phantom and stump pain, number of participants) on 3rd and 6th postoperative day and 6 months after surgery. Analgesic consumption reported at 24 and 72 h postoperatively, reported as medians. Postoperative central sensitisation on 3rd and 6th day postoperatively. AEs
Surgery type	Above or below knee amputation
Group numbers after end of study (treatment/control)	22/23
Age of patient population (treatment/control)	68.7 ± 12.2 68.9 ± 10.9
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Hayes 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	A random-number generator
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn in the immediate postoperative period
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Helmy 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 100% women
Interventions	Ketamine 0.3 mg/kg bolus IV before induction of anaesthesia
Outcomes	Pain intensity (VAS) reported at 2, 6, 12 and 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. Sedation level. PONV. Time to first analgesic request
Surgery type	Elective caesarean section
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	Median (range) 33 (24-43) 30 (22-41)
Notes	The authors declare that there is no conflict of interest
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Helmy 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation not sufficiently described Quote: "using a sealed envelope method, parturients were randomly assigned into 3 groups"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method described in detail
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described (only said "double blind")
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	19 and 20 participants per treatment arm

Hercock 1999

Study characteristics	
Methods	Randomised, double-blind. Intraoperative IV ketamine vs placebo/postoperative ketamine vs morphine
Participants	N = 50, 100% women
Interventions	Ketamine 0.3 mg/kg bolus IV after induction. Postoperative IV PCA 1 mg/bolus
Outcomes	Pain intensity. PCA morphine consumption. Outcomes reported at 24 h postoperatively
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	24/25
Age of patient population (treatment/control)	45.7 45.8
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	Authors' judgement	Support for judgement

Hercock 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Low risk	An independent anaesthetist, who subsequently had no role in the care of the participant, prepared the study drugs. Allocation was concealed in sealed, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	24 and 25 participants per treatment arm

Hu 2014

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 78, about 19% women
Interventions	Pre-incisional ketamine 0.1 mg/kg bolus IV followed by an infusion 2 µg/kg/min for 72 h
Outcomes	Pain intensity (NRS) reported on the 1st 7 postoperative days and at 2 and 6 months after surgery. Analgesic consumption reported at 72 h postoperatively. AEs. Evaluation of chronic postoperative pain
Surgery type	Muscle-sparing axillary thoracotomy
Group numbers after end of study (treatment/control)	31/47
Age of patient population (treatment/control)	51.39 ± 9.85 48.28 ± 13.95
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Hu 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only mentioned "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	31 and 47 participants per treatment arm

Ilkjaer 1998

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 38% women
Interventions	Ketamine 10 mg bolus IV before surgical incision + 10 mg/h infusion IV for 48 h postoperatively
Outcomes	Pain intensity (VAS) at rest and during movement, reported at 4, 6, 8 h, then beginning at 22nd postoperative h every 2 h up to 32 h postoperatively, then at 46 and 48 h postoperatively. Number of PCA morphine doses at 0-24 h and 24-48 h postoperatively. Pressure pain detection threshold at 0, 6, 22, 30 and 46 h postoperatively. Pain sensitivity. AEs
Surgery type	Elective nephrectomy or operation on pelvic structures
Group numbers after end of study (treatment/control)	24/28
Age of patient population (treatment/control)	Median age 50 (43-68) 55 (50-65)
Notes	Supported by a grant from the Danish Medical Council (Reg. no. 28809), Novo Nordisk Foundation, Danish Foundation for the Advancement of Medical Science and Agnes and Poul Friis Foundation
Risk of bias	

Ilkjaer 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Low risk	Quote: "Study drugs (ketamine 10 mg/ml) and placebo (isotonic saline) were prepared under sterile conditions by the hospital pharmacy in identical containers, marked with the name of the project, the investigator's name and consecutive patient number"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only stated "double-blind" but blinding process not described in detail
Incomplete outcome data (attrition bias) All outcomes	High risk	13% was withdrawn from the study and completed participants were analysed
Selective reporting (reporting bias)	Unclear risk	Insufficient information (precise numbers) of some outcomes, only reported P values
Size	High risk	24 and 28 participants per treatment arm

Jaksch 2002

Study characteristics	
Methods	Randomised, double-blind, placebo-control
Participants	N = 30, 50% women
Interventions	S-ketamine 0.5 mg/kg bolus IV before incision + infusion 2 µg/kg/min until 2 h after emergence from anaesthesia
Outcomes	Pain intensity (VAS) and PCA morphine consumption reported at 1, 24, 48, 72 and 120 h postoperatively. Time to first request for analgesia
Surgery type	Elective arthroscopic anterior cruciate ligament repair
Group numbers after end of study (treatment/control)	15/15
Age of patient population (treatment/control)	30 ± 8 33 ± 7
Notes	No mention of sponsorship or funding
Risk of bias	

Jaksch 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Low risk	Quote: "Envelopes containing identification of the preparation administered were available for emergencies"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Nurses not involved in the study prepared study solutions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	15 participants per treatment arm

Javery 1996

Study characteristics	
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 42, about 10% women
Interventions	Postoperative IV PCA ketamine 1 mg/bolus
Outcomes	Pain intensity (VAS). PCA morphine consumption. AEs. Outcomes reported at 24 h postoperatively
Surgery type	Lumbar microdiscectomy
Group numbers after end of study (treatment/control)	22/20
Age of patient population (treatment/control)	37.3 ± 9.9 39.5 ± 7.2
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Javery 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 and 22 participants per treatment arm

Jendoubi 2017

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, of whom 40 participants in IV ketamine and control treatment arms. 50% women
Interventions	At the induction of anaesthesia, ketamine bolus 0.15 mg/kg IV followed by infusion of 0.1 mg/kg/h for 24 h postoperatively
Outcomes	Cumulative morphine consumption reported every 6 h up to 24 h postoperatively. Pain intensity (VAS) at rest and during movement and coughing every 6 h up to 24 h and at 48 h postoperatively. AEs
Surgery type	Open nephrectomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	55.8 ± 13.5 48.3 ± 13.5
Notes	No sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Jendoubi 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described in detail. Only stated "randomised"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only mentioned that a nurse not participating in the study prepared study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Joly 2005

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 75, of whom 50 participants in IV ketamine and control treatment arms. 64% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + 5 µg/kg/min infusion IV until skin closure, then 2 µg/kg/min during the initial 48 postoperative hours
Outcomes	Pain intensity (VAS) reported at 24 and 48 h postoperatively. Analgesic consumption reported at 48 h postoperatively. AEs. Hyperalgesia on day 1 and 2 postoperatively
Surgery type	Major abdominal surgery
Group numbers after end of study (treatment/control)	24/25
Age of patient population (treatment/control)	59 ± 13 56 ± 12
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Joly 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Allocation concealed in sealed, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Joseph 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 53% women
Interventions	Ketamine 0.5 mg/kg bolus IV at anaesthesia induction + IV infusion 3 µg/kg/min during surgery, then 1.5 µg/kg/min for 48 h postoperatively
Outcomes	Pain intensity (NRS). Cumulative epidural ropivacaine consumption. Supplemental IV analgesia requirement. AEs. Outcomes reported on admission to PACU, at 12, 24, 48 h and 1 and 3 months after surgery
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	22/25
Age of patient population (treatment/control)	median age (range) 60 (24-80) 60 (31-79)
Notes	No mention of sponsorship or funding
Risk of bias	

Joseph 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to one of the two groups using a computer-generated randomization schedule."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only described that a hospital pharmacist dispensed study drugs that were identical in appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn
Selective reporting (reporting bias)	Low risk	Results of predefined outcomes reported
Size	High risk	22 and 25 participants per treatment arm

Kafali 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 48% women
Interventions	Pre-incisional ketamine 0.15 mg/kg bolus IV
Outcomes	Pain intensity (VAS) reported at 30 min, then 2, 12, 24 and 48 h postoperatively. Time to first analgesic demand. Analgesic consumption reported at 48 h postoperatively. Adverse effects
Surgery type	Lower abdominal surgery
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	47.2 ± 4.2 45.2 ± 3
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Kafali 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	A random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described, mentioned "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described, only mentioned "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Not all predefined outcomes are reported (adverse effects: pruritus)
Size	High risk	30 participants per treatment arm

Kakinohana 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 50, 58% women
Interventions	Pre-incisional ketamine bolus 1 mg/kg IV + infusion 1 mg/kg/h IV, maintained until 2 mg/kg administered
Outcomes	Pain intensity (VAS) reported at 5, 24 and 48 h postoperatively. Cumulative PCEA volume consumed reported at 5 h, 5-24 h, 24-48 h and at 48 h postoperatively. AEs
Surgery type	Elective open cholecystectomy
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	48.1 ± 10.1 49.9 ± 12.0
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Kakinohana 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment accomplished by blinded nurses
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Kamal 2008

Study characteristics	
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 80, about 49% women
Interventions	Postoperative IV PCA Ketamine 1 mg /mL
Outcomes	Pain intensity (VAS). Analgesic consumption. Adverse effects. Pain outcomes reported every 8 h up to 48 h postoperatively
Surgery type	Upper abdominal surgery
Group numbers after end of study (treatment/control)	40/40
Age of patient population (treatment/control)	38 ± 14 39 ± 12
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described

Kamal 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A nurse not involved in the care of participants prepared study drug syringes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Results of predefined outcomes reported
Size	High risk	40 participants per treatment arm

Kapfer 2005

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 65, of whom 43 participants in IV ketamine and control treatment arms. About 37% women
Interventions	Postoperative ketamine 10 mg bolus over a twelve-min period. IV if preceding opioid analgesia insufficient
Outcomes	Morphine consumption. Failure of morphine titration to produce adequate analgesia. Delay between the end of morphine titration and reappearance of a VRS pain score 2 or more
Surgery type	Laparotomy, lumbotomy, orthopedic surgery (hip or knee arthroplasty)
Group numbers after end of study (treatment/control)	22/21
Age of patient population (treatment/control)	51 ± 13 49 ± 15
Notes	Different types of surgery included. Supported by NIH Grant GM 061655 (Bethesda, MD), the Gheens Foundation (Louisville, KY), the Joseph Drown Foundation (Los Angeles, CA), and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list

Kapfer 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomization was based on computer-generated codes that were maintained in sequentially numbered, opaque envelopes until just before use."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22 and 21 participants per treatment arm

Karaman 2006

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 100% women
Interventions	1. Pre-incisional ketamine 0.4 mg/kg bolus IV 2. Ketamine 0.4 mg/kg bolus IV at wound closure
Outcomes	Pain intensity (VAS, VRS). Analgesic consumption. Time to first analgesic request. AEs. Pain outcomes reported at 1, 2, 3, 4, 8, 12 and 24 h postoperatively
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	40/20
Age of patient population (treatment/control)	48.2 ± 5.3 46.4 ± 3.5
Notes	Article in Turkish. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation achieved by shuffling envelopes

Karaman 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Kararmaz 2003

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40, 80% women
Interventions	Ketamine 0.5 mg/kg bolus IV + 0.5 mg/kg/h IV infusion until skin closure
Outcomes	Pain intensity (VAS) reported at 0.5, 1, 2, 4, 6, 12, 24 and 48 h postoperatively. Mean PCEA analgesic consumption on 1st and 2nd postoperative day. Time to first analgesic request. AEs
Surgery type	Elective renal surgery
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	36.7 ± 13.8 38.2 ± 15.4
Notes	No mention of funding or sponsorship

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described

Kararmaz 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Karcioglu 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40, gender of participants not presented in demographic data
Interventions	Ketamine 1 mg/kg bolus IV at anaesthesia induction + 25 mcg/kg/min IV infusion until the end of surgery
Outcomes	Pain intensity (VAS) reported at PACU discharge and at 24 h postoperatively. Analgesic consumption reported as proportion (%) of participants receiving analgesics. AEs
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	17/20
Age of patient population (treatment/control)	38.6 ± 11.7 43.4 ± 12.1
Notes	No mention of sponsorship or funding. The authors declare no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described

Karcioglu 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported (three participants withdrawn from the ketamine group because of hypertension)
Size	High risk	17 and 20 participants per treatment arm

Katz 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 168, 100% men
Interventions	1. Pre-incisional ketamine 0.2 mg/kg bolus IV + 0.0025 mg/kg/min infusion IV for 70 mins 2. Ketamine 0.2 mg/kg bolus IV 70 mins after the incision + 0.0025 mg/kg/min infusion IV up to 80 mins
Outcomes	Pain intensity (VAS), reported at 3, 6, 12, 24, 48 and 72 h postoperatively. Analgesic consumption reported at 0-3, 3-6, 6-12, 12-24, 24-48 and 48-72 h postoperatively. Touch and pain threshold (von Frey)
Surgery type	Radical prostatectomy
Group numbers after end of study (treatment/control)	97/46
Age of patient population (treatment/control)	62 ± 6.8 61 ± 6.7
Notes	The study was supported by Grants MT-12052 and MOP-37845 from the Canadian Institutes of Health Research (CIHR), Ontario, Canada, and a CIHR Investigator Award to the lead author.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Quote: "An opaque envelope containing the patient number and group assignment was prepared, sealed and numbered for each patient by the hospital pharmacist" (a third party)

Katz 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	11% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	47, 46 and 50 participants per treatment arm

Kim 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 47% women
Interventions	1. Pre-incisional ketamine 0.5 mg/kg bolus IV + 1 mcg/kg/min intraoperative infusion IV until 48 h postoperatively 2. Pre-incisional ketamine 0.5 mg/kg bolus IV + 2 mcg/kg/min intraoperative infusion IV until 48 h postoperatively
Outcomes	Pain intensity (VAS) reported at 1, 6, 12 and 24 h postoperatively. Analgesic consumption reported at 48 h postoperatively. AEs
Surgery type	Lumbar spinal fusion surgery
Group numbers after end of study (treatment/control)	35/17
Age of patient population (treatment/control)	55.5 ± 11.8 56 ± 13
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described

Kim 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	12% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	High risk	18, 17 and 17 participants per treatment arm

Kim 2016

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 58, 95% women
Interventions	After the induction on anaesthesia, ketamine bolus 1 mg/kg IV followed by a continuous infusion 60 µg/kg/h until skin closure
Outcomes	Pain intensity (NRS). Analgesic consumption. Pain outcomes reported at 1, 6, 24 and 48 h postoperatively. AEs
Surgery type	Bilateral axillo-breast approach robotic or endoscopic thyroidectomy
Group numbers after end of study (treatment/control)	28/29
Age of patient population (treatment/control)	40 ± 9 39 ± 8
Notes	No mention of sponsorship or funding. The study authors have no conflicts of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated table of random numbers (Random-Allocation Software Version 1.0)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail

Kim 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel collected data
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	28 and 29 participants per treatment arm

Köse 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 150, of whom 120 participants in IV ketamine and control treatment arms. About 74% women
Interventions	Ketamine 0.1 mg/kg OR ketamine 0.25 mg/kg OR ketamine 0.5 mg/kg bolus IV 20 mins before the end of surgery. Heterogeneous surgery types
Outcomes	Pain intensity (VAS) reported at 0, 1 and 2 h postoperatively. Time to first analgesic request. AEs. Postoperative shivering
Surgery type	Various operations under general anaesthesia
Group numbers after end of study (treatment/control)	90/30
Age of patient population (treatment/control)	41.2 ± 12 44.5 ± 9.2
Notes	Primary endpoint was postoperative shivering. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Low risk	Allocation in closed envelopes, identical study drug syringes prepared and labelled by an independent investigator not participating in the further study

Köse 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded investigator made assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Kudoh 2002

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 70. Participants diagnosed as having major depression. Gender of participants not presented
Interventions	Pre-incisional ketamine 1 mg/kg bolus IV
Outcomes	Pain intensity (VAS) reported every 8 h for the first 24 h, then every 24 h till 4th postoperative day. Postoperative confusion
Surgery type	Orthopedic surgery
Group numbers after end of study (treatment/control)	35/35
Age of patient population (treatment/control)	46.9 ± 8.8 48.2 ± 7.4
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias)	Low risk	Blinded participants

Kudoh 2002 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	35 participants per treatment arm

Kwok 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 135, 100% women
Interventions	1. Pre-incisional bolus of ketamine 0.15 mg/kg IV 2. At wound closure: ketamine bolus 0.15 mg/kg IV
Outcomes	Pain intensity (VAS) reported hourly up to 7 h postoperatively, then at 24 h. Analgesic consumption until VAS < 20 mm. AEs
Surgery type	Laparoscopic gynaecological surgery
Group numbers after end of study (treatment/control)	90/45
Age of patient population (treatment/control)	33 ± 6.1 34 ± 6
Notes	No mention of sponsorship or funding
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel

Kwok 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	45 participants per treatment arm

Kwon 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40, 100% women
Interventions	Intraoperative ketamine 0.3 mg/kg bolus IV followed by an infusion 3 µg/kg/min
Outcomes	Pain intensity (VAS) reported at 24 and 48 h postoperatively. Analgesic consumption reported at 0-6 h, 6-12 h, 12-24 h and 24-48 h postoperatively. AEs
Surgery type	Mastectomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	50.5 ± 8.8 47.2 ± 7.4
Notes	Article in Korean. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in detail

Kwon 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Size	High risk	20 participants per treatment arm

Lahtinen 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 102, about 11% women
Interventions	S-ketamine 75 µg/kg bolus IV immediately after anaesthesia induction + intraoperative IV infusion 1.25 µg/kg/min for 48 h after arrival to the PACU
Outcomes	Pain intensity (VAS) reported after extubation, after titration of oxycodone until VAS < 30 mm, on the day of surgery at 12 pm, on first postoperative day at 8 am, 4 pm and 12 pm, on second postoperative day at 8 pm and 4 pm. Cumulative analgesic consumption at 48 h postoperatively. AEs
Surgery type	Sternotomy
Group numbers after end of study (treatment/control)	44/46
Age of patient population (treatment/control)	59 ± 5 58 ± 7
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with a computer program by using random numbers and a balanced design."
Allocation concealment (selection bias)	Low risk	Mentioned: "the code remained blinded until the end of the study" and that study drug syringes were identical in appearance but not described in detail how the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias)	Low risk	Blinded personnel

Lahtinen 2004 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	11% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported adequately
Size	High risk	44 and 46 participants per treatment arm

Lak 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 12% women
Interventions	Ketamine 0.5 mg/kg bolus IV postoperatively + IV infusion 2 µg/kg/min for 24 h, then 1 µg/kg/min the following 24 h
Outcomes	Pain intensity (VAS and face pain scale) reported hourly during the first 4 h, then at 8, 12, 24 and 48 h postoperatively. Analgesic consumption reported at 48 h postoperatively. AEs
Surgery type	Nephrectomy
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	27.3 ± 5.5 27.9 ± 3.9
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was assigned to patients of the two groups according to random numbers table"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double blind" but not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding process not described

Lak 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	20% was withdrawn
Selective reporting (reporting bias)	High risk	Pain outcome not reported using predefined pain scale (face pain scale)
Size	High risk	25 participants per treatment arm

Leal 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 40, about 83% women
Interventions	Ketamine 5 µg/kg/min infusion IV until wound closure
Outcomes	Pain intensity (NRS) reported every 30 min up to 4 h, then every 6 h up to 24 h postoperatively. Time to the first analgesic supplementation. Cumulative analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	46 ± 12.5 45.5 ± 16.1
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation achieved by drawing envelopes
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias)	Low risk	No withdrawals

Leal 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	AEs are defined and reported in 'results' section, but not predefined in 'methods' section
Size	High risk	20 participants per treatment arm

Leal 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 56, about 84% women
Interventions	Ketamine 5 µg/kg/min infusion IV until skin closure
Outcomes	Pain intensity (NRS) reported in 30-min intervals up to 4 h, then in 6-h intervals up to 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. Time to first morphine supplementation. Extent of hyperalgesia reported at 24 h after surgery. AEs
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	28/28
Age of patient population (treatment/control)	45.8 ± 13.1 43.4 ± 15.9
Notes	Funded by grant 2009/5335-4, São Paulo Research Foundation and Coordenacão de Aperfeicoamento de Pessoal De Nível Superior

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation achieved by a computer program "Randomizer"
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes contained allocation information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Binded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn

Leal 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Adverse effects not defined in 'methods' section but are reported
Size	High risk	28 participants per treatment arm

Lebrun 2006

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 84, about 42% women
Interventions	1. Ketamine 0.3 mg/kg bolus IV at anaesthesia induction 2. Ketamine 0.3 mg/kg bolus IV at the end of surgery
Outcomes	Pain intensity (VAS) reported at 0.5, 1, 2, 4, 24 and 48 h postoperatively. Time to first request for analgesia. AEs. Analgesic consumption in PACU
Surgery type	Third molar surgical removal
Group numbers after end of study (treatment/control)	54/30
Age of patient population (treatment/control)	19 ± 6.7 20.7 ± 8.7
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described in detail. Only mentioned that a nurse not involved in the study prepared study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel and participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	13% was withdrawn

Lebrun 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	31, 23 and 30 participants per treatment arm

Lee 2008

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 32, about 55% women
Interventions	Pre-incisional ketamine 0.15 mg/kg bolus IV
Outcomes	Pain intensity (NRS) reported on arrival to PACU and at 5, 10, 15 and 30 min, then at 5 and 24 h postoperatively. Analgesic consumption (either ketorolac or tramadol) reported as additional count per day
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	16/15
Age of patient population (treatment/control)	40.7 ± 7.8 43.8 ± 10.8
Notes	Article in Korean. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study authors do not describe randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described, only stated "double blind" in the title
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A blinded investigator assessed postoperative pain scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available

Lee 2008 *(Continued)*

Size	High risk	16 and 15 participants per treatment arm

Lehmann 2001

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 80, about 58% women
Interventions	Pre-incisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS, VRS). PCA piritramide consumption. Rescue medication. AEs. Pain outcomes reported hourly up to 6 h postoperatively, then at 12 and 24 h after surgery
Surgery type	Laparotomy or proctologic surgery
Group numbers after end of study (treatment/control)	40/40
Age of patient population (treatment/control)	46 ± 12 43 ± 10
Notes	In the English abstract, the operation is laparoscopic surgery, in the original article (in German), it is said to be laparotomy. We contacted the study author and he clarified that the procedure was laparotomy or proctologic surgery. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A person not involved in patient care prepared the study solutions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported. Results as percentage

Lehmann 2001 *(Continued)*

Size	High risk	40 participants per treatment arm

Lenzmeier 2008

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 22, 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV at anaesthesia induction
Outcomes	Pain intensity (VAS) reported upon admission to and at discharge from PACU. Opioid consumption during PACU stay
Surgery type	Laparoscopic abdominal procedures
Group numbers after end of study (treatment/control)	11/11
Age of patient population (treatment/control)	29.7 ± 8.5 31.6 ± 6.7
Notes	A pilot study, findings reported as descriptive statistics. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentioned "double-blind" but blinding process not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	11 participants per treatment arm.

Lin 2016

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	90, 100% women
Interventions	Pre-incisional ketamine 0.3 mg/kg bolus IV
Outcomes	Pain intensity (VAS) reported at 2, 6, 12 and 24 h postoperatively. Mean analgesic dose per participant. Time to first analgesic request. AEs
Surgery type	Gynecological laparoscopic surgery
Group numbers after end of study (treatment/control)	30/29
Age of patient population (treatment/control)	39.6 ± 9.8 43.4 ± 10.1
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only mentioned double-blind with no further description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	High risk	Results of time to first request for analgesia are reported but this outcome was not predefined in methods
Size	High risk	29 and 30 participants per treatment arm

Lo 2008

Study characteristics	
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 30, 100% women
Interventions	Ketamine 2 mg /bolus via IV-PCA postoperatively
Outcomes	Pain intensity (VAS) reported at 24 h and 48 h postoperatively. Analgesic consumption reported at 48 h postoperatively. AEs
Surgery type	Abdominal hysterectomy
Group numbers after end of study (treatment/control)	15/15 Basis for group size unclear (power analysis not presented). Study authors state that the study was underpowered because of cessation of the recruitment by a labour disruption
Age of patient population (treatment/control)	Mean values without standard deviations reported 49.2 47.4
Notes	Study not sufficiently powered because of interruption by a labour disruption. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation achieved by selecting envelopes
Allocation concealment (selection bias)	Low risk	Group allocation was enclosed in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Time frame for mean analgesic consumption unclear
Size	High risk	15 participants per treatment arm

Loftus 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 101, about 40% women
Interventions	Ketamine 0.5 mg/kg bolus IV on anaesthesia induction + infusion 10 µg/kg/min IV until wound closure
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Outcomes reported at 24 and 48 h, and 6 weeks
Surgery type	Major lumbar spine surgery
Group numbers after end of study (treatment/control)	52/50
Age of patient population (treatment/control)	51.7 ± 14.2 51.4 ± 14.4
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation scheme
Allocation concealment (selection bias)	Low risk	The study infusions were prepared by the investigational pharmacy (a third party) preoperatively and labelled as "study drug/placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of the data pertaining to the primary outcome were missing in the final analysis. Missing data were due to unanticipated early participant discharge with equal numbers in both treatment groups. No participants enrolled in the study were excluded from the primary analysis
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	Unclear risk	50 and 52 participants per treatment arm

Mahran 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 90, of whom 60 participants in IV ketamine and control treatment arms. 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV before anaesthesia induction + intraoperative IV infusion 0.25 mg/kg/h till the end of skin closure
Outcomes	Pain intensity (VAS) reported at 30 min, 2, 4, 6, 12 and 24 h postoperatively. Cumulative analgesic consumption at 24 h. AEs
Surgery type	Breast cancer surgery (radical mastectomy)
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	53.1 ± 6.2 53.9 ± 8.1
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number assignment
Allocation concealment (selection bias)	Low risk	Allocation concealed in sequentially numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All predefined dropouts reported
Size	High risk	30 participants per treatment arm

Martinez 2014

Study characteristics

Martinez 2014 *(Continued)*

Methods	Randomised, double-blind. Ketamine vs placebo. Ketamine vs pregabalin
Participants	N = 142. Total hip arthroplasty under general anaesthesia. About 48% women
Interventions	Ketamine 0.5 mg/kg bolus IV at induction + 3 µg/kg/min IV infusion until skin closure
Outcomes	Pain intensity (NRS) reported in the recovery room, at 24 and 48 h. Analgesic consumption at 48 h. Pressure pain threshold measured on the first and second postoperative days. AEs
Surgery type	Total hip arthroplasty
Group numbers after end of study (treatment/control)	Ketamine: 34 Placebo: 38 Ketamine + pregabalin 35 Pregabalin: 35
Age of patient population (treatment/control)	60 ± 17 64 ± 11 64 ± 9 59 ± 12
Notes	Divided into 2 for analysis: ketamine vs placebo and ketamine + pregabalin vs pregabalin. No external funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation concealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study solutions were prepared by an independent person.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	13% was withdrawn
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported adequately
Size	High risk	34, 38, 35 and 35 participants per treatment arm.

Mathisen 1999

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 82% women
Interventions	1. Pre-incisional bolus of R-ketamine 1 mg /kg IV 2. IV-bolus of R-ketamine 1 mg/kg at wound closure
Outcomes	Pain intensity (VAS, VRS) reported at 1, 2, 3, 4 and 24 h and 7 days after surgery. PCA opioid consumption reported at 1, 2, 3 and 4 h postoperatively. Analgesics after discharge. AEs
Surgery type	Elective laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	32/18
Age of patient population (treatment/control)	48 ± 15.8 50 ± 13
Notes	No mention of sponsorship or funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Low risk	Central allocation Quote: "The hospital pharmacy prepared the drugs in identical ampules marked with patient number and injection number in a randomized, double-blind manner."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	17% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

McKay 2007

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 41, about 46% women
Interventions	Pre-incisional ketamine 1.5 mg/kg bolus IV followed by ketamine infusion 2.5 µg/kg/min
Outcomes	Pain intensity (VAS; reported as AUC: units (cm) x half days). AEs. Return of bowel function. Time to ambulation. Length of hospital stay. Analgesic consumption reported as total opioid use for each study participant, time frame unclear
Surgery type	Laparotomy (bowel resection)
Group numbers after end of study (treatment/control)	19/22
Age of patient population (treatment/control)	49.5 ± 16.3 51.8 ± 12.8
Notes	Primary outcome was return of bowel function. The study was funded in part by a grant from the Royal University Hospital Foundation, Saskatoon, Canada

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Central allocation. Hospital pharmacy (a third party) randomised participants and prepared study drug solutions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	19 and 22 participants per treatment arm

Mebazaa MS 2008

Study characteristics	
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 138, about 49% women
Interventions	Ketamine 1 mg/bolus IV via PCA
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Outcomes reported every 4 h up to 48 h postoperatively
Surgery type	Laparotomy
Group numbers after end of study (treatment/control)	67/67
Age of patient population (treatment/control)	46 ± 13 46 ± 14
Notes	No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to the type of surgery (i.e. visceral or gynaecological) and performed according to a table of random numbers per blocks of six
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	Unclear risk	67 participants per treatment arm

Mendola 2012

Study characteristics

Mendola 2012 *(Continued)*

Methods	Randomised, double-blind, placebo control
Participants	N = 66, about 32% women
Interventions	S-ketamine 0.1 mg/kg/h infusion IV during surgery and for 60 h postoperatively
Outcomes	Pain intensity (NRS) on 1st, 2nd and 3rd day postoperatively and then monthly up to 6 months. Analgesic consumption reported on 1st, 2nd and 3rd days postoperatively. AEs. NPSI at 1, 3 and 6 months postoperatively
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	32/30
Age of patient population (treatment/control)	62 ± 10.4 65.7 ± 10.9
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation achieved by the statistic laboratory of the institution
Allocation concealment (selection bias)	Low risk	Central allocation. Hospital pharmacy (a third party) prepared the study infusions that were coded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes addressed
Size	High risk	32 and 30 participants per treatment arm

Menigaux 2000

Study characteristics

Methods	Randomised, double-blind, placebo control

Menigaux 2000 *(Continued)*

Participants	N = 45, about 33% women
Interventions	Ketamine 0.15 mg/kg bolus IV before surgical incision or at wound closure
Outcomes	Pain intensity (VAS, VRS) reported at 1, 2, 3 h, then every 4 h up to 48 h after surgery. PCA morphine consumption. Incremental doses reported hourly up to 3 h postoperatively, then every 4 h up to 48 h. Cumulative morphine consumption reported at 24 and 48 h after surgery. AEs. Time to first analgesic request
Surgery type	Elective arthroscopic anterior cruciate ligament repair
Group numbers after end of study (treatment/control)	30/15
Age of patient population (treatment/control)	26 ± 6 28 ± 7
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel at data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes clearly reported
Size	High risk	15 participants per treatment arm

Menigaux 2001

Study characteristics	
Methods	Randomised, double-blind, placebo control

Menigaux 2001 *(Continued)*

Participants	N = 50, 34% women
Interventions	Pre-incisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS, VRS) reported every 15 mins for 1 h, then every 2 h up to 6 h after surgery and on 1st, 2nd and 3rd day after surgery. Rescue medication (mean number of analgesic tablets per participant required during 3 days). AEs
Surgery type	Outpatient knee arthroscopy
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	37 ± 9 36 ± 12
Notes	Supported by NIH Grant GM 58273, the Joseph Drown Foundation, and the Commonwealth of Kentucky Research Challenge Trust Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Michelet 2007

Study characteristics

Methods	Randomised, double-blind. Ketamine + morphine vs morphine

Michelet 2007 *(Continued)*

Participants	N = 50, 28% women
Interventions	Ketamine 1 mg/mL via IV PCA
Outcomes	Pain intensity (VAS) and cumulative analgesic consumption, reported at baseline, at 12, 24, 36, 48 and 60 h postoperatively. AEs
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	24/24
Age of patient population (treatment/control)	Mean (range) 64 (42-77) 63 (42-76)
Notes	No financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only mentioned that a hospital pharmacist prepared study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% was withdrawn
Selective reporting (reporting bias)	Low risk	Results of predefined outcomes reported
Size	High risk	24 participants per treatment arm

Miziara 2016

Study characteristics

Methods	Randomised, double-blind, placebo control

Miziara 2016 *(Continued)*

Participants	N = 48, patient demographic data table not presented
Interventions	S-ketamine infusion 5 µg/kg/min beginning 5 mins before surgery and lasting till the end of surgery
Outcomes	Pain intensity (VNS 0-10) reported during PACU stay, at 4 and 12 h postoperatively. Analgesic consumption reported during PACU stay, at 4-12 h and as cumulative analgesic consumption at 12 h postoperatively. AEs
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	24/21
Age of patient population (treatment/control)	No data available
Notes	No mention of sponsorship or funding. Study authors state that they have no conflicts interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation achieved using a randomisation software
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed in sequentially numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	21 participants per treatment arm

Murdoch 2002

Study characteristics

Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N = 42, 100% women

Murdoch 2002 *(Continued)*

Interventions	Postoperative IV PCA ketamine 0.75 mg/bolus + morphine
Outcomes	Pain intensity (VRS), reported every 4 h up to 16 h postoperatively, then at 24 h. PCA morphine consumption reported at 24 h. AEs
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	21/19
Age of patient population (treatment/control)	43.2 ± 6.6 41.8 ± 8.8
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes reported but only P values
Size	High risk	21 and 19 participants per treatment arm

Nesek-Adam 2012

Study characteristics

Methods	Randomised, double-blind
Participants	N = 80, about 73% women
Interventions	1. Pre-incisional ketamine 0.15 mg/kg bolus IV vs placebo

Nesek-Adam 2012 *(Continued)*

	2. Pre-incisional ketamine 0.15 mg/kg + diclofenac 1 mg/kg bolus IV vs pre-incisional diclofenac 1 mg/kg IV
Outcomes	Pain intensity (VAS), reported every 2 h up to 6 h postoperatively, then at 12 and 24 h. Time to first analgesic request. AEs
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	20/20/20/20
Age of patient population (treatment/control)	Ketamine group 50.7 ± 11.9 Placebo group 53.6 ± 9.6 Diclofenac group 45.7 ± 15.3 Ketamine + diclofenac group 52.7 ± 15.5
Notes	4 treatment arms. Ketamine vs placebo and ketamine + diclofenac vs diclofenac. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number table
Allocation concealment (selection bias)	Low risk	Quote: "An envelope containing group assignment was prepared, sealed, and numbered for each patient."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Nielsen 2017

Study characteristics	
Methods	Randomised, double-blind, placebo control

Nielsen 2017 *(Continued)*

Participants	N = 150, 65% women
Interventions	Intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 mg/kg/h
Outcomes	Analgesic consumption, reported at the first hour in the PACU and then at 24 h. Postoperative pain intensity (VAS), reported every 2 h up to 24 h postoperatively at rest and during mobilisation. AEs (PONV reported every 6 h up to 24 h postoperatively, CNS AEs reported as number of participants experiencing CNS adverse event during 0-24 h). Persistent pain 6 months postoperatively
Surgery type	Lumbar fusion surgery
Group numbers after end of study (treatment/control)	75/75
Age of patient population (treatment/control)	57 ± 14 55 ± 13
Notes	The study was supported by the Department of Neuroanesthesiology Rigshospitalet, Glostrup, Copenhagen University Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Central allocation. Hospital pharmacy (a third party) prepared and pre-packed identical ampoules in consecutively numbered boxes according to the computer-generated randomisation list. Information about each participant's treatment was concealed in consecutively numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn in the immediate postoperative period
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	Unclear risk	75 participants per treatment arm

Ögün 2001

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 47, 100% women
Interventions	Ketamine 1 mg/kg bolus IV pre-incisionally and after excision of tissue specimen
Outcomes	Pain intensity (VAS, VRS) reported at 0, 1, 2, 4, 6, 12 and 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Mastectomy
Group numbers after end of study (treatment/control)	16/15
Age of patient population (treatment/control)	47.2 ± 12.7 47.8 ± 14.2
Notes	Article in Turkish. No mention of sponsorship or funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment process not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only mentioned double-blind but lacks description of how it was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned double-blind but lacks description of how it was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	15 and 16 participants per treatment arm

Ong 2001

Study characteristics

Ong 2001 *(Continued)*

Methods	Randomised, double-blind, placebo control
Participants	N = 40, gender of participants not specified
Interventions	Ketamine 0.3 mg/kg bolus IV prior to induction
Outcomes	Pain intensity (VAS) reported on arrival to PACU, at 1 h postoperatively and on discharge. Analgesic requirement during PACU stay. AEs
Surgery type	Extraction of wisdom teeth
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	24.1 ± 15.3 24.1 ± 6.6
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by drawing cards from an envelope
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Ozhan 2013

Study characteristics

Methods	Randomised, double-blind, placebo control

Ozhan 2013 *(Continued)*

Participants	N = 60, about 82% women
Interventions	Pre-incisional ketamine 0.25 mg/kg bolus IV
Outcomes	Analgesic consumption at 24 h postoperatively. Preoperative and postoperative cognitive function (Mini-Mental Test). AEs. Recovery time
Surgery type	Laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	46 ± 12.3 47 ± 11.5
Notes	No mention of sponsorship or funding. The study authors declare that they have no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Pacreu 2012

Study characteristics

Methods	Randomised, double-blind. Intraoperative ketamine + postoperative IV-PCA containing ketamine + methadone VS intraoperative placebo + postoperative IV-PCA with methadone alone

Pacreu 2012 *(Continued)*

Participants	N = 22, 70% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + intraoperative ketamine 2.5 µg/kg/min infusion IV + post-operative IV-PCA 0.5 mg/bolus
Outcomes	Pain intensity (NRS). Analgesic consumption. AEs Main outcomes at 24 and 48 h
Surgery type	Lumbar arthrodesis
Group numbers after end of study (treatment/control)	10/10
Age of patient population (treatment/control)	52.9 ± 12.6 61.3 ± 11.7
Notes	Institutional support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was performed by the Department of Biostatistics
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	10 participants per treatment arm

Papaziogas 2001

Study characteristics

Methods	Randomised, double-blind. Ketamine IV + ropivacaine SC vs ropivacaine SC

Papaziogas 2001 *(Continued)*

Participants	N = 55, of whom 35 participants in IV ketamine and control treatment arms
Interventions	Pre-incisional bolus of ketamine 1 mg/kg IV
Outcomes	Pain intensity (VAS, VRS) reported at baseline, at 3, 6, 12, 24 and 48 h postoperatively. Analgesic consumption reported at 48 h postoperatively. Rescue analgesia. Time to first request for analgesia. AEs
Surgery type	Elective laparoscopic cholecystectomy
Group numbers after end of study (treatment/control)	18/17
Age of patient population (treatment/control)	41.3 ± 13.6 47.9 ± 16.7
Notes	Third group received saline IV and saline SC. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding process not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding process not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	18, 17 and 18 participants per treatment arm

Parikh 2011

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 38% women

Parikh 2011 *(Continued)*

Interventions	Ketamine 0.15 mg/kg bolus IV 30 min before start of surgery + 2 µg/kg/min infusion IV till start of skin closure
Outcomes	Pain intensity (VAS), reported at 15, 30 and 60 min after surgery, then every 4 h up to 16 h and finally at 24 h postoperatively. Time to first analgesic request. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Open renal surgery by flank incision
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	39.2 ± 12.2 42.2 ± 10.5
Notes	No financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by shuffling envelopes
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Patel 2016

Study characteristics

Methods	Randomised, double-blind. Ketamine + clonidine vs clonidine
Participants	N = 75, of whom 50 participants in IV ketamine and control treatment arms. 10% women

Patel 2016 *(Continued)*

Interventions	Ketamine 1 mg/kg bolus IV during induction of anaesthesia
Outcomes	Pain intensity (VAS) reported at 4, 8, 12 and 24 h postoperatively. Analgesic consumption reported as number of doses at 24 h. Intraoperative haemodynamic parameters
Surgery type	Off-pump coronary artery bypass
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	60.91 ± 6.17 58.52 ± 8.29
Notes	No funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Pirim 2006

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 45, 100% women
Interventions	Postoperative ketamine infusion initially 10 mg/kg/min IV and gradually lowered to 2.5 mg/kg/min for 24 h postoperatively

Pirim 2006 *(Continued)*

Outcomes	Pain intensity (VAS, VRS). Analgesic consumption. Pain outcomes reported at 1, 2, 4, 6, 12 and 24 h post-operatively. AEs reported at 24 and 48 h postoperatively
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	23/22
Age of patient population (treatment/control)	46.7 ± 6 45.9 ± 5.5
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail
Allocation concealment (selection bias)	Low risk	Allocation concealed in envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments made by a researcher who was unaware of the study groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22 and 23 participants per treatment arm

Remérand 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 154, 49% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + 2 µg/kg/min infusion IV for 24 h
Outcomes	Pain intensity (NRS) reported on 1st and 2nd day postoperatively. Analgesic consumption reported at PACU, at 24 and 48 h postoperatively and on days 4 and 7 postoperatively. AEs

Remérand 2009 *(Continued)*

Surgery type	Total hip arthroplasty
Group numbers after end of study (treatment/control)	79/75
Age of patient population (treatment/control)	64 ± 13 65 ± 14
Notes	Supported by institutional and/or departmental sources

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation process
Allocation concealment (selection bias)	Low risk	Quote: "Before the study began, as part of a computer-generated randomization process, 160 identical white envelopes were prepared, numbered, and sealed by a person external to our clinical unit. Each envelope contained detailed instructions of the preparation of 2 syringes (ketamine or saline)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals in the immediate postoperative period. At 6 months, 8% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	Unclear risk	79 and 74 participants per treatment arm

Reza 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV before anaesthesia induction
Outcomes	Pain intensity (VAS), reported at 2, 6, 12 and 24 h postoperatively. Analgesic consumption, reported at 0-2 h and 2-24 h postoperatively. AEs

Reza 2010 *(Continued)*

Surgery type	Elective caesarean section
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	27 ± 5.1 27 ± 4.5
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes adequately addressed
Size	High risk	30 participants per treatment arm

Roytblat 1993

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 22, 100% women
Interventions	Pre-incisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS, VRS). PCA morphine consumption. Time to first request for analgesia. AEs. Pain outcomes recorded at 1, 2, 3, 4, 5, 6, 12 and 24 h after surgery
Surgery type	Elective open cholecystectomy

Roytblat 1993 *(Continued)*

Group numbers after end of study (treatment/control)	11/11
Age of patient population (treatment/control)	55.1 ± 10.7 54.8 ± 14.8
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and personnel involved in patient management were unaware of the group to which the participant had been assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel involved in data collection were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	11 participants per treatment arm

Safavi 2011

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 120, of whom 60 participants in IV ketamine and control treatment arms. About 48% women
Interventions	Pre-incisional ketamine 1 mg/kg bolus IV
Outcomes	Pain intensity (VAS), reported at 15 and 30 min, then at 1, 2, 3, 4, 8, 12 and 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. Time to first request for rescue analgesia. AEs
Surgery type	Open cholecystectomy

Safavi 2011 *(Continued)*

Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	47.7 ± 11.8 54.1 ± 11.3
Notes	Four study groups in the study: 1 group where participants received ketamine IV, 2 groups where ketamine was given SC in different doses and 1 control group where the participants received saline. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Low risk	A research nurse prepared envelopes that were sealed, numbered and stored in a box
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcome adequately addressed
Size	High risk	30 participants per treatment arm

Sahin 2004

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 47, of whom 33 participants in IV ketamine and control treatment arms. About 52% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS), reported in 15-min intervals during the 1st h. Cumulative analgesic consumption reported at 24 h postoperatively. Time to first analgesic request. AEs
Surgery type	Lumbar discectomy

Sahin 2004 *(Continued)*

Group numbers after end of study (treatment/control)	17/16
Age of patient population (treatment/control)	46.5 ± 7.3 48.3 ± 11.2
Notes	3 study groups. The treatment group received ketamine bolus IV + remifentanil intraoperatively. The 2nd group where participants received saline bolus IV + remifentanil intraoperatively served as a control group. The 3rd group (14 participants) received saline bolus IV + saline infusion intraoperatively and was excluded from the analysis. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes reported but misses exact numbers of PONV, only mentioned that the incidences of nausea, vomiting were similar among groups
Size	High risk	17 and 16 participants per treatment arm

Sen 2009

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, 100% women
Interventions	Pre-incisional ketamine 0.3 mg/kg bolus IV + 0.05 mg/kg/h infusion IV until the end of surgery
Outcomes	Pain intensity (VRS). Analgesic consumption. AEs. Main outcomes reported every 4 h up to 24 h postoperatively
Surgery type	Abdominal hysterectomy

Sen 2009 *(Continued)*

Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	46 ± 6 46 ± 7
Notes	The third group in this study was treated with oral gabapentin. Supported by institutional and departmental sources at GATA Haydarpasa Eğitim Hastanesi.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Central allocation: hospital pharmacy (a third party) prepared study drugs that were labelled identically
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported adequately
Size	High risk	20 participants per treatment arm

Siddiqui 2015

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, gender of participants not specified
Interventions	Ketamine 0.3 mg/kg bolus IV following induction
Outcomes	Pain intensity (VAS) reported at 30 min postoperatively as number of participants with VAS-score 1-3, 4-5, 6-8 and 9-10, respectively. Analgesic consumption during recovery room stay. AEs
Surgery type	Elective day care surgery (procedures not defined)

Siddiqui 2015 *(Continued)*

Group numbers after end of study (treatment/control)	29/29
Age of patient population (treatment/control)	36.1 ± 10.6 36.1 ± 9
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described in detail
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding method not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding method not described in detail
Incomplete outcome data (attrition bias) All outcomes	High risk	Discrepancy between text, "there were no dropouts" and a results table
Selective reporting (reporting bias)	High risk	All predefined outcomes are not reported (rescue analgesia)
Size	High risk	29 participants per treatment arm

Singh 2013

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 80. Only mentioned that adult patients of either gender were randomised
Interventions	1. Pre-incisional ketamine 1 mg/kg bolus IV 2. Pre-incisional ketamine 0.75 mg/kg bolus IV 3. Pre-incisional ketamine 0.5 mg/kg bolus IV
Outcomes	Pain intensity (VAS), reported every 30 min for first 2 h, every 1 h for the next 4 h, and then at 12 h and 24 h postoperatively. Time to first request for analgesia. Analgesic consumption, reported as mean number of analgesic doses given to participants in different groups. AEs
Surgery type	Laparoscopic cholecystectomy

Singh 2013 *(Continued)*

Group numbers after end of study (treatment/control)	20/20/20/20
Age of patient population (treatment/control)	NA
Notes	3 groups with 3 different ketamine doses given pre-incisionally IV vs placebo. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation was concealed in sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	Unclear risk	No numerical results but percentages reported. Withdrawals not reported
Size	High risk	20 participants per treatment arm

Snijdelaar 2004

Study characteristics

Methods	Randomised, double-blind. Intraoperative S-ketamine vs placebo/postoperative S-ketamine + morphine vs morphine and placebo
Participants	N = 28. Radical retropubic prostatectomy. 100% men
Interventions	Intraoperative S-ketamine 0.1 mg/kg bolus IV followed by a continuous infusion of 2 µg/kg/min IV until skin closure + postoperative IV PCA S-ketamine 0.5 mg/bolus
Outcomes	Pain intensity (VAS) reported hourly up to 4 h, then at 8 and 12 h, then every 6 h up to 48 h postoperatively. PCA morphine consumption, reported hourly during the first 4 h, then every 6 h up to 48 h postoperatively. Hyperalgesia (pain perception threshold, pressure algometry). AEs
Surgery type	Radical retropubic prostatectomy

Snijdelaar 2004 *(Continued)*

Group numbers after end of study (treatment/control)	13/12
Age of patient population (treatment/control)	60.1 ± 4.7 61.7 ± 4.7
Notes	Dr D G Snijdelaar is supported by an Independent Investigator Grant from Parke-Davis (now Pfizer). Dr J. Katz is supported by a Canada Research Chair in Health Psychology at York University from the Canadian Institutes of Health Research.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by using the random function of Microsoft EXCEL 97
Allocation concealment (selection bias)	Low risk	Central allocation. Study syringes prepared and dispensed by the hospital pharmacy (a third party). Coded syringes that were prepared in a blinded fashion for each participant and retained by the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel prepared study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel collected data
Incomplete outcome data (attrition bias) All outcomes	High risk	11% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	13 and 12 participants per treatment arm

Song 2013

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 50, 100% women
Interventions	Ketamine 0.3 mg/kg bolus IV at induction + postoperative IV-PCA with ketamine 3 mg/kg, background infusion 2 mL/h + 2 mL/bolus on-demand
Outcomes	Pain intensity (VAS) reported at 0-6 h, 6-12 h, 12-24 h, 24-36 h and 36-48 h postoperatively. Cumulative volume of IV-PCA consumed reported at 6, 12, 24, 36 and 48 h postoperatively. AEs

Song 2013 *(Continued)*

Surgery type	Lumbar spinal fusion
Group numbers after end of study (treatment/control)	24/25
Age of patient population (treatment/control)	Mean (range) 57 (30-65) 58 (34-65)
Notes	Financial support provided from departmental sources

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Low risk	Results of predefined outcomes reported
Size	High risk	24 and 25 participants per treatment arm

Song 2014

Study characteristics	
Methods	Randomised, double-blind
Participants	N = 75, 100% women
Interventions	Pre-incisional ketamine 0.25 mg/kg bolus IV followed by an infusion of 5 µg/kg/min until skin closure
Outcomes	Pain intensity (VAS), reported at 1 h postoperatively. Cumulative analgesic consumption reported at 24 h postoperatively. Time to first request for analgesia. Hyperalgesia reported at 24 h postoperatively

Song 2014 *(Continued)*

Surgery type	Laparoscopic gynaecologic surgery
Group numbers after end of study (treatment/control)	25/25
Age of patient population (treatment/control)	48.9 ± 6.8 49.3 ± 5.7
Notes	The study was supported by Wonkwang University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants unaware of group assignments. Not described whether anaesthesiologists in the operating room were blinded, thus unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded anaesthesiologist assessed pain
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	25 participants per treatment arm

Spreng 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 83, 58% women of those included
Interventions	Pre-incisional S-ketamine 0.35 mg/kg bolus IV + 5 µg/kg/min infusion IV until 2 mins after the end of surgery
Outcomes	Pain intensity (VAS). Emergence time. AEs Main measurements were 1 day, 7 days, and 3 months

Spreng 2010 *(Continued)*

Surgery type	Ambulatory haemorrhoidectomy
Group numbers after end of study (treatment/control)	39/38
Age of patient population (treatment/control)	46.4 ± 4.7 61.7 ± 4.7
Notes	Institutional funding, with no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation by the hospital pharmacy. Quote: "Permuted block randomization, blinding and packing of the study medication were performed by the hospital pharmacy. The randomization codes were provided in sealed envelopes which only were opened in case of emergency or after completion of the study protocol of all study participants."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% was withdrawn
Selective reporting (reporting bias)	Unclear risk	Study authors state that treatment group had more AEs. However, the difference was not statistically significant
Size	High risk	39 and 38 participants per treatment arm

Stubhaug 1997

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 20, 50% women
Interventions	Ketamine 0.5 mg/kg bolus IV + infusion 2 µg/kg/min IV for 24 h, thereafter 1 mcg/kg/min and maintained for 48 h

Stubhaug 1997 *(Continued)*

Outcomes	Pain intensity (VAS) reported hourly during the first 4 h. Cumulative PCA morphine consumption reported at 0-24 h, 24-48 h and 48-72h postoperatively. Area of punctate hyperalgesia reported on days 1, 3 and 7 postoperatively. Pressure pain threshold. AEs
Surgery type	Nephrectomy (live kidney donors)
Group numbers after end of study (treatment/control)	10/10
Age of patient population (treatment/control)	Median (range) 44 (32-53) 42 (25-66)
Notes	Baxter Norway provided Baxter Ambulatory PCA Pumps with printer. No mention of additional funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers (Moses Oakford algorithm)
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation remained concealed to patients and investigators during the whole study. Study drug for each patient was prepared by the hospital pharmacy in identical containers, marked with consecutive patient numbers only and delivered by a portable pump via a separate i.v. line."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	10 participants per treatment arm

Subramaniam 2011

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 38, 50% women

Subramaniam 2011 *(Continued)*

Interventions	Ketamine 0.1 mg/kg bolus IV at anaesthesia induction + 2 µg/kg/min intraoperative infusion IV and 24 h postoperatively
Outcomes	Pain intensity (VAS) and analgesic consumption reported at 1, 2, 4, 8, 12, 18, 24, 36 and 48 h postoperatively. AEs
Surgery type	Lumbar or thoracolumbar laminectomy and fusion
Group numbers after end of study (treatment/control)	15/15
Age of patient population (treatment/control)	57.2 ± 12.2 56.5 ± 13.6
Notes	The study was underpowered. According to power analysis, 26 participants per study group should have been recruited in order to obtain sufficient power. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central allocation. Randomisation and allocation concealment by the hospital pharmacy (a third party)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	21% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes adequately reported
Size	High risk	15 participants per treatment arm

Suzuki 1999

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 140, about 38% women
Interventions	IV-bolus of ketamine at wound closure:

Suzuki 1999 *(Continued)*

	1. 50 µg/kg 2. 75 µg/kg 3. 100 µg/kg
Outcomes	Pain intensity (VAS) reported at 15-min intervals for the first hour. Rescue medication, reported as mean amount needed during the phase 1 recovery. AEs
Surgery type	Elective outpatient surgery (inguinal hernia repair, excision of skin lesions, breast or lymph node biopsy)
Group numbers after end of study (treatment/control)	105/35
Age of patient population (treatment/control)	36 ± 11 30 ± 12
Notes	3 different doses of ketamine IV vs placebo. 35 participants in each study group. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A person not involved in the study prepared study drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	35 participants per treatment arm. Heterogeneous procedures

Suzuki 2006

Study characteristics	
Methods	Randomised, double-blind, placebo control

Suzuki 2006 *(Continued)*

Participants	N = 50, about 41% women
Interventions	Ketamine 5 µg/kg/min IV infusion after tracheal intubation lasting 72 h after surgery
Outcomes	Pain intensity (VAS) reported at 6, 12, 24 and 48 h postoperatively. Cumulative analgesic consumption reported at 0-6 h, 6-12 h, 12-24 h and 24-48 h after surgery. Abnormal sensation of pain around the wound on postoperative day 7. AEs.
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	24/25
Age of patient population (treatment/control)	66 ± 14 66 ± 9
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to one of two groups using a computer-generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only stated that the study drugs were prepared and placed in the infusion pump by an investigator who did not participate in the administration of anaesthesia or the evaluation of postoperative pain.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% was withdrawn
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes reported. Epidural infusion was suspended in some participants (ketamine 3, control 5) due to hypotension.
Size	High risk	24 and 25 participants per treatment arm

Tena 2014

Study characteristics

Methods	Randomised, double-blind, placebo control

Tena 2014 *(Continued)*

Participants	N = 125, of whom 68 participants in IV ketamine and control treatment arms. About 28% women
Interventions	Pre-incisional ketamine 0.5 mg/kg bolus IV + postoperatively 0.25 mg/kg/h infusion IV for 48 h
Outcomes	Pain intensity (VAS) reported at 2, 4, 24 and 72 h and 3 days, 3 months and 6 months postoperatively. Hyperalgesia (von Frey filaments, electronic von Frey, electrical toothbrush) reported at 72 h, 7 days, 3 months and 6 months postoperatively. AEs
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	33/35
Age of patient population (treatment/control)	62.9 ± 9.8 66.5 ± 9.9
Notes	The 3rd study group was not included in analysis because participants received ketamine epidurally. No mention of sponsorship or funding and the authors declare no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	17% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	33 and 35 participants per treatment arm

Ünlügenc 2003

Study characteristics

Methods	Randomised, double-blind. Ketamine + morphine vs morphine

Ünlügenc 2003 *(Continued)*

Participants	N = 90, of whom 60 participants in IV ketamine and control treatment arms. About 43% women
Interventions	Postoperative IV PCA ketamine 0.0125 mg/kg/bolus + morphine
Outcomes	Pain intensity (VRS). PCA morphine consumption. Pain outcomes reported at 15 and 30 min, then at 1, 2, 6, 12 and 24 h postoperatively. AEs
Surgery type	Major abdominal surgery
Group numbers after end of study (treatment/control)	30/28
Age of patient population (treatment/control)	52 ± 4 51 ± 1.1
Notes	3 study groups in this study. We excluded the 3rd group from the analysis because the participants also received magnesium sulphate and the 2 other study groups did not. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% was withdrawn
Selective reporting (reporting bias)	High risk	All predefined AEs are not reported
Size	High risk	30, 28 and 29 participants per treatment arm

Van Elstraete 2004

Study characteristics

Methods	Randomised, double-blind, placebo control

Van Elstraete 2004 *(Continued)*

Participants	N = 40, 50% women
Interventions	Ketamine 0.5 mg/kg bolus IV after anaesthesia induction + 2 µg/kg/min infusion IV till the end of surgery
Outcomes	Pain intensity (VAS). Analgesic consumption. Time to first request for analgesia. AEs Main outcomes at 2, 4, 8, 12, and 24 h postoperatively
Surgery type	Elective tonsillectomy
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	29 ± 7 29 ± 10
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to one of two groups using a table of computer-generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail. Only stated that a research nurse not involved in the perioperative care of the participant prepared and labelled 2 syringes per randomisation list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The anaesthetist who was in charge of the patient during surgery was unaware of the study group assignment, as were those involved in data collection."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The anaesthetist who was in charge of the patient during surgery was unaware of the study group assignment, as were those involved in data collection."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	20 participants per treatment arm

Webb 2007

Study characteristics	
Methods	Randomised, double-blind, placebo control

Webb 2007 *(Continued)*

Participants	N = 120, about 38% women
Interventions	Ketamine 0.3 mg/kg bolus IV at anaesthesia induction + intraoperative infusion 0.1 mg/kg/h for 48 h after surgery
Outcomes	Pain intensity (VRS) and analgesic consumption reported every 4 h up to 48 h postoperatively. AEs. Subjective analgesic efficacy
Surgery type	Laparotomy
Group numbers after end of study (treatment/control)	52/58
Age of patient population (treatment/control)	63 ± 15 61 ± 15
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to treatment group was determined in advance according to tables of random numbers and concealed from patients and hospital staff, using sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	Unclear risk	56 and 64 participants per treatment arm

Woo 2014

Study characteristics

Methods	Randomised, double-blind, placebo control

Woo 2014 *(Continued)*

Participants	N = 40, about 33% women
Interventions	Pre-incisional ketamine 0.3 mg/kg bolus IV + continuous infusion 0.15 mg/kg/min until 5 mins before the end of surgery
Outcomes	Pain intensity (NRS). Analgesic consumption. Pain outcomes reported at 1, 6, 12, 24, 36 and 48 h post-operatively. AEs
Surgery type	Arthroscopic shoulder surgery
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	42.9 ± 19 50 ± 14.1
Notes	No mention of sponsorship or funding. The study authors declare no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by a computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Only said that an anaesthetist blinded to group assignments prepared study drugs but no further description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Size	High risk	20 participants per treatment arm

Wu 2009

Study characteristics

Methods	Randomised, double-blind
Participants	N = 30, about 27% women

Wu 2009 *(Continued)*

Interventions	Perioperative ketamine infusion 0.08 mg/kg/h IV with morphine for 50 h vs morphine alone
Outcomes	Pain intensity (VAS) reported at 4, 8, 20 and 24 h postoperatively. Analgesic consumption at 0-8 h, 8-24 h, 24-48 h after surgery (median values). Cumulative analgesic consumption at 48 h postoperatively. AEs
Surgery type	Elective radical operation for oesophageal carcinoma
Group numbers after end of study (treatment/control)	15/15
Age of patient population (treatment/control)	56 ± 11 58 ± 10
Notes	Article in Chinese. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentioned "double blind" but blinding not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mentioned "double blind" but blinding not described in detail
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals
Selective reporting (reporting bias)	High risk	Predefined observer's assessment of awareness/sedation scores not provided
Size	High risk	15 participants per treatment arm

Yalcin 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 90, 100% women
Interventions	Ketamine 0.5 mg/kg bolus IV before anaesthesia induction + 5 µg/kg/min infusion IV until skin closure

Yalcin 2012 *(Continued)*

Outcomes	Pain intensity (VAS). Analgesic consumption. AEs Main outcomes at 2, 4, 6, 12 and 24 hrs postoperatively
Surgery type	Total abdominal hysterectomy
Group numbers after end of study (treatment/control)	26/27
Age of patient population (treatment/control)	48.3 ± 5.7 48.1 ± 6
Notes	The 3rd group that received paracetamol as study drug was excluded from analysis No financial or competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number system
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observer
Incomplete outcome data (attrition bias) All outcomes	High risk	12% was withdrawn
Selective reporting (reporting bias)	Unclear risk	Exact numbers of AEs not reported
Size	High risk	26 and 27 participants per treatment arm

Yamauchi 2008

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 202, about 30% women
Interventions	1. Ketamine 1 mg/kg bolus IV at skin incision + 42 µg/kg/h infusion IV for 24 h

Yamauchi 2008 *(Continued)*

	2. Ketamine 1 mg/kg bolus IV at skin incision + 83 µg/kg/h infusion IV for 24 h
Outcomes	Pain intensity (VAS) at rest and during movement at 1, 6, 12, 24, 36, 48 h and 3, 6 and 10 days after surgery. Analgesic consumption. AEs
Surgery type	Posterior cervical spine and lumbar spine surgery
Group numbers after end of study (treatment/control)	133/67
Age of patient population (treatment/control)	60.2 ± 16.9 57 ± 17.3
Notes	The study consists of cervical and lumbar surgery participants with 2 different interventions and corresponding control groups. These treatment arms (4 treatment arms and corresponding control groups) were analysed separately. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by shuffling envelopes
Allocation concealment (selection bias)	Low risk	Allocation concealment in envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentioned "double-blind" but not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	22, 23 and 23 participants in the cervical surgery groups. 42, 46 and 44 participants in the lumbar surgery groups

Yazigi 2012

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 52% women

Yazigi 2012 *(Continued)*

Interventions	Pre-incisional ketamine 0.1 mg/kg bolus IV + 0.05 mg/kg/h infusion IV during surgery and for 72 h post-operatively
Outcomes	Pain intensity (VAS) reported every 6 h for 3 days postoperatively. Cumulative analgesic requirement reported at 72 h. AEs
Surgery type	Thoracotomy
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	57.3 ± 11.9 56.9 ± 12.5
Notes	No financial support or funding and no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Central allocation by the hospital pharmacy (a third party). Study drugs were prepared in identical containers and marked with the name of the study and a consecutive number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Yeom 2012

Study characteristics

Methods	Randomised, double-blind. Ketamine + fentanyl vs fentanyl
Participants	N = 40, 70% women

Yeom 2012 *(Continued)*

Interventions	Ketamine 0.2 mg/kg bolus IV + 30 µg/mL/kg infusion IV intraoperatively
Outcomes	Pain intensity (NRS). AEs. Ketamine and fentanyl infusion rates. Outcomes recorded at 1, 24 and 48 h after surgery
Surgery type	Lumbar spinal fusion
Group numbers after end of study (treatment/control)	20/20
Age of patient population (treatment/control)	61 ± 10 64.5 ± 11.5
Notes	No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded personnel prepared study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	High risk	Not all AEs are reported that were predefined in methods
Size	High risk	20 participants per treatment arm

Ysasi 2010

Study characteristics	
Methods	Randomised, double-blind, placebo control
Participants	N = 60, about 30% women
Interventions	Ketamine infusion 8 µg/kg/min IV during surgery

Ysasi 2010 *(Continued)*

Outcomes	Pain intensity (VAS, SVS) reported at 15 and 30 mins, then 1, 2, 4, 6, 8, 12 and 24 h postoperatively. Analgesic consumption reported at 24 h postoperatively. AEs
Surgery type	Myocardial revascularisation
Group numbers after end of study (treatment/control)	30/30
Age of patient population (treatment/control)	62.2 ± 10 63.3 ± 9.6
Notes	Article in Spanish. No mention of sponsorship or funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
Size	High risk	30 participants per treatment arm

Zakine 2008

Study characteristics

Methods	Randomised, double-blind, placebo control
Participants	N = 81, 23% women
Interventions	1. Pre-incisional ketamine 0.5 mg/kg bolus IV + 2 µg/kg/min infusion IV during surgery 2. Pre-incisional ketamine 0.5 mg/kg bolus IV + 2 µg/kg/min infusion IV during surgery and for 48 h postoperatively

Zakine 2008 *(Continued)*

	Heterogeneous procedures
Outcomes	Pain intensity (VAS). Analgesic consumption. AEs. Pain outcomes recorded at 4, 24 and 48 h after surgery
Surgery type	Major abdominal, urologic or vascular surgery
Group numbers after end of study (treatment/control)	50/27
Age of patient population (treatment/control)	median (interquartile range) 63 (12) 62 (14)
Notes	Various procedures. Supported by a grant from the French Ministry of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by means of computer-generated opaque envelopes containing the patient number and group assignment."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentioned "double-blind" but blinding not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mentioned "double-blind" but blinding not described in detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% was withdrawn
Selective reporting (reporting bias)	Low risk	Predefined outcomes adequately reported
Size	High risk	27, 23 and 27 participants per treatment arm

AEs: adverse events;**ED:** epidural, **ICDSC:** intensive care delirium screening checklist, **h:** hour(s), **ICU:** intensive care unit, **IV:** intravenous, **mcg:** micrograms, **mg:** milligrams, **min:** minutes, **kg:** kilograms, **N:** number of participants, **NPRS:** numeric pain rating scale, **NPSI:** neuropathic pain symptom inventory, **NRS:** numerical rating scale, **PACU:** post-anaesthesia care unit, **PCA:** patient-controlled analgesia, **PCEA:** patient-controlled epidural analgesia, **PONV:** post-operative nausea and vomiting; **PTPS:** post-thoracotomy pain syndrome; **SC:** subcutaneous; **VAS:** visual analogue scale, **VNS:** verbal numeric scale; **VRS:** verbal rating scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrishamkar 2012	Open-label study
Adams 2003	Open-label study
Aghamohammadi 2012	Inappropriate method - study compared 3 different active treatment regimens, with no placebo
Akca 2016	Inappropriate method - pain measured but not reported, except as a binary outcome at short post-operative time scales
Avidan 2017	Inappropriate method - different anaesthesia techniques
Behdad 2011	Open-label study
Bentley 2005	Inappropriate method - number of participants in each study group was not reported
Bilgin 2005	Inappropriate method - all participants treated with ketamine
Clausen 1975	Inappropriate pain scale (measurement)
Edwards 1993	Number of participants who completed the study fewer than 10
Gillies 2007	Inappropriate method - mixed population of adults and children
Guan 2008	Number of participants who completed the study fewer than 10
Heinke 1999	Inappropriate method - the primary outcome was PCA consumption of piritramide, but fixed maximum dose of piritramide limited the utility of the study to detect differences
Hong 2011	Open-label study
Ito 1974	Open-label study
Jahangir 1993	Inappropriate method - time with study drug infusion varied, and so groups may not have been comparable in ketamine dose
Jensen 2008	Inappropriate method - no general anaesthesia
Jiang 2016	Pain scores were not reported in any detail (measurement)
Joachimmson 1986	Inappropriate pain scale. Participants on ventilator and probably not able to communicate easily (measurement)
Kadic 2016	Inappropriate method - participants in the same study group received ketamine and pregabalin so effects of ketamine could not be identified
Kim 2001	Inappropriate description of methods - not described and may not be blinded
Kim 2005	Open-label study
Kollender 2008	Open-label study
Kose 2008	No pain or analgesic consumption outcome reported (measurement)
Launo 2004	Inappropriate method - ketamine was compared to tramadol with no placebo

Study	Reason for exclusion
Lee 2005	Open-label study
Lee 2006	Inappropriate description of methods - not described and may not be blinded
Lee 2013	Open-label study
Lee 2014	Open-label study
Liang 2006	Inappropriate description of methods - not described and may not be blinded
Lux 2009	Inappropriate randomisation - participants divided sequentially into 2 groups
Malek 2006	Inappropriate method - outcome is chronic pain
Maurset 1989	Number of participants who completed the study fewer than 10
Nayar 2009	Open-label study
Ndoye 2008	Not an RCT
Nesher 2008	Inappropriate randomisation. Participants assigned to 1 of 2 groups according to their national ID-number
Nesher 2009	Inappropriate randomisation. Randomisation according to the national ID-number
Nikolayev 2008	Open-label study
Nitta 2013	Open-label study
Nourozi 2010	Inappropriate method - mixed population of adults and children
Oliveira 2005	Inappropriate method - all participants treated with ketamine
Owen 1987	Inappropriate method - not placebo-controlled
Park 2004	Methods not described and may not be blinded
Perrin 2009	Number of participants in group who completed the study fewer than 10
Reeves 2001	Inappropriate method - different PCA settings for different participants, so non-standardised treatment regimens
Sadove 1971	Inappropriate method - not IV ketamine administration
Sollazzi 2008	Open-label study
Song 2004	Methods not described and may not be blinded
Sveticic 2008	Inappropriate method - different anaesthesia techniques (general anaesthesia, regional anaesthesia or combined)
Talu 2002	Inappropriate method - not IV
Thomas 2012	Open-label study

Study	Reason for exclusion
Tverskoy 1994	Number of participants in group who completed the study fewer than 10
Tverskoy 1996	Number of participants in group who completed the study fewer than 10
Ünlügenc 2002	Inappropriate method - different PCA settings for different participants
Urban 2008	Open-label study
Weinbroum 2003	Inappropriate randomisation - participants allocated into 1 of the 2 treatment protocols on alternate days
Wilder-Smith 1998	Inappropriate method - study compared 3 different treatment regimens without a placebo comparator group
Xie 2003	Inappropriate method - placebo administered epidurally, so no comparison group for IV ketamine
Xu 2017	Inappropriate method - no general anaesthesia

ID-number: identification number, **IV:** intravenous; **PCA:** patient-controlled analgesia; **RCT:** randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Lee 2018

Methods	A prospective, randomised, double-blind, placebo-controlled study
Participants	N = 64, robotic thyroidectomy
Interventions	Pre-incisional ketamine 0.15 mg/kg IV followed by a continuous infusion 2 mcg/kg/min until the end of procedure
Outcomes	Primary endpoint: pain intensity (VAS) at 6 h postoperatively. Secondary outcomes: pain intensity (VAS) at 0, 1, 24 and 48 h and at 3 months postoperatively at rest and while coughing. Incidence of hypoesthesia, time administration of the first analgesic, number of participants requiring additional analgesics, complications related to opioids or ketamine
Notes	Results for pain outcomes are provided as median (IQR) thus cannot be used in meta-analysis. AEs are reported as N (%)

Lou 2017

Methods	Prospective, randomised study
Participants	N = 66. Mastectomy
Interventions	Ketamine 0.5 mg/kg infused in 1 h daily for 7 days vs saline (NaCl 0.9%)
Outcomes	Postoperative pain (VAS) during PACU, 4 h, 24 h and 2-5 days after surgery. Analgesic requirement at same time points. Hospital Anxiety and Depression Scale (HADS) 5 days after surgery. Incidence of postmastectomy pain syndrome, pain site and HADS at 3 and 6 months after surgery
Notes	Original article is in Chinese. Only abstract available

Moon 2018

Methods	Not known.
Participants	N = 46. Laparoscopic hysterectomy
Interventions	Pre-incisional ketamine 1 mg/kg IV followed by a continuous infusion 0.5 mg/kg/h vs saline (NaCl 0.9%)
Outcomes	Primary outcome: mechanical pain threshold evaluating hyperalgesia. Secondary outcomes: postoperative pain (VAS). Analgesic and antiemetic consumption. Incidence of dizziness
Notes	Only abstract available

AEs: adverse events; **IQR:** interquartile range,**h:** hour/s, **IV:** intravenous, **kg:** kilograms, **mcg:** micrograms, **mg:** milligrams, **min:** minutes, **N:** number of participants, **PACU:** post-anaesthesia care unit; **VAS:** visual analogue scale

DATA AND ANALYSES

Comparison 1. Perioperative ketamine versus control in a non-stratified study population

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Opioid consumption at 24 hours	65	4004	Mean Difference (IV, Random, 95% CI)	-7.63 [-8.88, -6.39]
1.2 Opioid consumption at 48 hours	37	2449	Mean Difference (IV, Random, 95% CI)	-12.62 [-15.06, -10.18]
1.3 Pain intensity at rest at 24 hours	82	5004	Mean Difference (IV, Random, 95% CI)	-5.09 [-6.55, -3.64]
1.4 Pain intensity during movement at 24 hours	29	1806	Mean Difference (IV, Random, 95% CI)	-5.60 [-10.72, -0.48]
1.5 Pain intensity at rest at 48 hours	49	2962	Mean Difference (IV, Random, 95% CI)	-5.03 [-6.65, -3.40]
1.6 Pain intensity during movement at 48 hours	23	1353	Mean Difference (IV, Random, 95% CI)	-5.72 [-10.15, -1.29]
1.7 Time to first request for analgesia/trigger of PCA	31	1678	Mean Difference (IV, Random, 95% CI)	53.89 [37.00, 70.78]
1.8 CNS adverse events - all studies	105	6538	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.95, 1.43]
1.9 Hyperalgesia	7	333	Mean Difference (IV, Random, 95% CI)	-7.08 [-11.92, -2.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 CNS adverse events - studies with events	52	3706	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.95, 1.43]
1.11 Postoperative nausea and vomiting - all studies	95	5965	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]

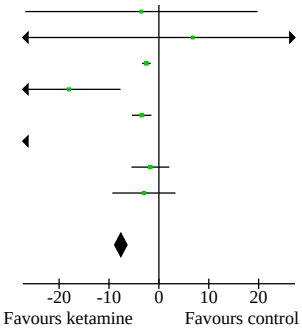
Analysis 1.1. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	19.4	10.7	15	30.7	15.9	15	1.0%	-11.30 [-21.00 , -1.60]
Argiriadou 2011	12.2	2.8	27	21	5	26	2.3%	-8.80 [-10.99 , -6.61]
Aubrun 2008	24.8	19.2	45	17.8	16.4	45	1.3%	7.00 [-0.38 , 14.38]
Aveline 2006	21.8	9.2	45	33.9	5.4	23	2.1%	-12.10 [-15.58 , -8.62]
Aveline 2009	39.2	6.5	25	56.8	5.9	24	2.1%	-17.60 [-21.07 , -14.13]
Ayoglu 2005	19.7	1.9	20	23.5	2.3	20	2.4%	-3.80 [-5.11 , -2.49]
Barreveld 2013	218	147	29	231	168	30	0.0%	-13.00 [-93.48 , 67.48]
Bilgen 2012	44	19	35	28	14	16	1.0%	16.00 [6.69 , 25.31]
Bilgen 2012	42.5	15.1	70	28	14	18	1.3%	14.50 [7.13 , 21.87]
Cenzig 2014	47	15.3	30	85.2	8.01	30	1.5%	-38.20 [-44.38 , -32.02]
Crousier 2008	13	6.6	12	16.17	26	18	0.7%	-3.17 [-15.75 , 9.41]
Dahi-Taleghani 2014	7	2	70	12	3	70	2.5%	-5.00 [-5.84 , -4.16]
Dahl 2000	19.2	6.3	29	20.4	8	60	2.2%	-1.20 [-4.26 , 1.86]
Dualé 2009	39	23	39	48	28	41	0.8%	-9.00 [-20.21 , 2.21]
Dullenkopf 2009	8.8	9	77	10.3	6.8	33	2.2%	-1.50 [-4.57 , 1.57]
Fiorelli 2015	18	0.4	38	22.5	0.3	37	2.5%	-4.50 [-4.66 , -4.34]
Ganne 2005	33.3	14.9	30	31.9	15.3	31	1.3%	1.40 [-6.18 , 8.98]
Garcia-Navia 2016	30.95	7.88	11	27.54	11.75	11	1.2%	3.41 [-4.95 , 11.77]
Garg 2016	2.45	2.1	22	15.64	9.3	22	2.0%	-13.19 [-17.17 , -9.21]
Gilabert Morell 2002	11.4	6.7	44	15.63	9.31	22	1.9%	-4.23 [-8.60 , 0.14]
Guignard 2002	42.7	16.3	25	64.9	27	25	0.7%	-22.20 [-34.56 , -9.84]
Guillou 2003	36	20	41	48	20	52	1.2%	-12.00 [-20.19 , -3.81]
Hadi 2010	35.2	8.9	30	60	2.6	15	2.1%	-24.80 [-28.25 , -21.35]
Hadi 2013	35.2	8.9	30	60	2.6	15	2.1%	-24.80 [-28.25 , -21.35]
Haliloglu 2015	25	3.7	26	36.4	3.6	26	2.3%	-11.40 [-13.38 , -9.42]
Hasanein 2011	40	6.1	30	47.4	8	30	2.1%	-7.40 [-11.00 , -3.80]
Helmy 2015	8.2	3.3	19	14	3.8	20	2.3%	-5.80 [-8.03 , -3.57]
Hercock 1999	34.5	15.2	24	33	16	25	1.1%	1.50 [-7.24 , 10.24]
Ilkjaer 1998	28	21	30	36	23	30	0.8%	-8.00 [-19.14 , 3.14]
Jaksch 2002	40.2	17	15	44.1	45	15	0.2%	-3.90 [-28.24 , 20.44]
Javery 1996	25.82	16.4	22	51.1	20.8	20	0.8%	-25.28 [-36.68 , -13.88]
Jendoubi 2017	10.7	2.3	20	15.9	1.7	20	2.4%	-5.20 [-6.45 , -3.95]
Kafali 2004	44.2	4.1	30	53.9	4	30	2.3%	-9.70 [-11.75 , -7.65]
Kamal 2008	33.3	7.4	40	46.9	7.4	40	2.1%	-13.60 [-16.84 , -10.36]
Karaman 2006	13.8	4.1	40	14.6	4.1	20	2.3%	-0.80 [-3.00 , 1.40]
Katz 2004	51.9	33.3	97	52.3	32.8	46	0.8%	-0.40 [-11.97 , 11.17]
Kwon 2009	13.3	4.5	20	16.9	11.5	20	1.7%	-3.60 [-9.01 , 1.81]
Leal 2013	29	18.4	20	25.1	13.3	20	1.0%	3.90 [-6.05 , 13.85]
Leal 2015	27.4	18.3	28	27.7	12.9	28	1.2%	-0.30 [-8.59 , 7.99]
Lehmann 2001	17.5	11.3	40	20.7	14.3	40	1.6%	-3.20 [-8.85 , 2.45]
Lin 2016	5.42	1.64	29	5.25	1.45	29	2.5%	0.17 [-0.63 , 0.97]
Loftus 2010	142	82	52	202	176	50	0.1%	-60.00 [-113.63 , -6.37]
Mahran 2015	23.1	6.91	30	34.43	10.14	30	1.9%	-11.33 [-15.72 , -6.94]
Menigaux 2000	26.2	17.9	30	49.7	24.2	15	0.6%	-23.50 [-37.32 , -9.68]
Michelet 2007	25.4	12.8	24	30.4	10.2	24	1.5%	-5.00 [-11.55 , 1.55]
Murdoch 2002	67.6	25.1	21	66.4	17.7	21	0.7%	1.20 [-11.94 , 14.34]
Nielsen 2017	79	47	74	121	53	73	0.5%	-42.00 [-58.20 , -25.80]
Ögün 2001	10.6	4.6	16	16.3	3.6	15	2.2%	-5.70 [-8.60 , -2.80]
Parikh 2011	5.8	1.48	30	18.1	1.8	30	2.5%	-12.30 [-13.13 , -11.47]
Remérand 2009	14	13	79	19	12	75	2.0%	-5.00 [-8.95 , -1.05]
Reza 2010	8	4.7	30	11.2	6.5	30	2.2%	-3.20 [-6.07 , -0.33]
Roytblat 1993	29.5	7.5	11	48.7	13	11	1.1%	-19.20 [-28.07 , -10.33]
Safavi 2011	2.33	0.6	30	15.1	5.3	30	2.3%	-12.77 [-14.68 , -10.86]
Sahin 2004	20.28	11.81	17	17.26	11.87	16	1.2%	3.02 [-5.06 , 11.10]
Sen 2009	28	8	20	48	17	20	1.2%	-20.00 [-28.23 , -11.77]
Snijdelaar 2004	32.15	18.59	13	50.42	24.7	12	0.4%	-18.27 [-35.52 , -1.02]
Song 2013	39.9	14.7	24	50.5	23.2	25	0.9%	-10.60 [-21.43 , 0.23]
Song 2014	23.23	0.76	25	24.04	0.92	25	2.5%	-0.81 [-1.28 , -0.34]
Stubhaug 1997	64.5	22.6	10	68	30	10	0.3%	-3.50 [-26.78 , 19.78]
Subramaniam 2011	103.6	87.8	15	96.8	67.85	15	0.0%	6.80 [-49.35 , 62.95]
Ünlügenc 2003	46.5	1.7	30	49	1.6	28	2.5%	2.50 [-3.35 , 1.65]

Analysis 1.1. (Continued)

Stubhaug 1997	64.5	22.6	10	68	30	10	0.3%	-3.50 [-26.78 , 19.78]
Subramaniam 2011	103.6	87.8	15	96.8	67.85	15	0.0%	6.80 [-49.35 , 62.95]
Ünlügenc 2003	46.5	1.7	30	49	1.6	28	2.5%	-2.50 [-3.35 , -1.65]
Webb 2007	25.3	23.3	52	43.3	31.9	59	0.9%	-18.00 [-28.31 , -7.69]
Woo 2014	14.1	3	20	17.55	3.3	20	2.3%	-3.45 [-5.40 , -1.50]
Yalcin 2012	35.34	13.71	26	73.03	22.41	27	1.0%	-37.69 [-47.65 , -27.73]
Ysasi 2010	23.1	7.3	30	24.8	7.7	30	2.0%	-1.70 [-5.50 , 2.10]
Zakine 2008	22.3	15.1	50	25.3	12.6	27	1.5%	-3.00 [-9.33 , 3.33]
Total (95% CI)			**2128**			**1876**	**100.0%**	**-7.63 [-8.88 , -6.39]**

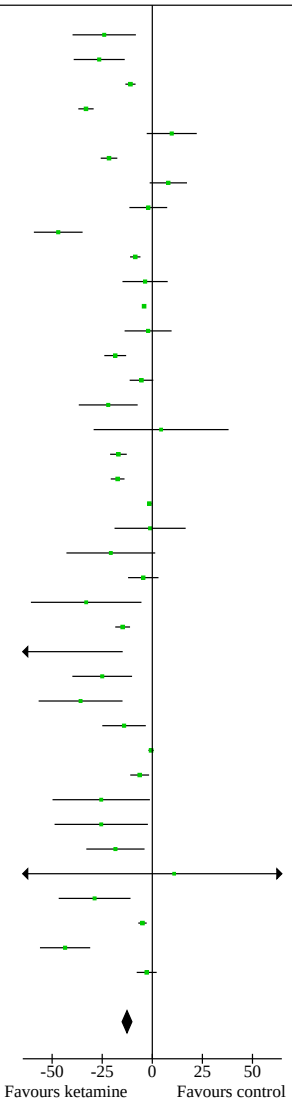
Heterogeneity: Tau² = 16.24; Chi² = 1634.83, df = 65 (P < 0.00001); I² = 96%
Test for overall effect: Z = 12.02 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 2: Opioid consumption at 48 hours

	Ketamine			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Adam 2005	45	20	20	69	30	20	1.6%	-24.00 [-39.80 , -8.20]	
Adriaenssens 1999	27.6	12.4	15	54.1	21.9	15	2.0%	-26.50 [-39.24 , -13.76]	
Argiriadou 2011	14.1	3.7	27	25	5.5	26	4.3%	-10.90 [-13.43 , -8.37]	
Arikan 2016	32.6	9.2	40	65.7	8.2	40	4.1%	-33.10 [-36.92 , -29.28]	
Aubrun 2008	59.6	31.1	45	49.9	29.3	45	2.1%	9.70 [-2.78 , 22.18]	
Aveline 2009	50.5	5.7	25	72.1	8.7	24	4.0%	-21.60 [-25.74 , -17.46]	
Bilgen 2012	46	19	35	38	14	16	2.7%	8.00 [-1.31 , 17.31]	
Bilgen 2012	44	14.7	70	46	19	18	2.7%	-2.00 [-11.43 , 7.43]	
Bornemann-Cimenti 2016	62.1	19.95	37	109.05	22.95	19	2.1%	-46.95 [-59.11 , -34.79]	
Choi 2015	22.51	3.81	25	31.02	5.39	25	4.3%	-8.51 [-11.10 , -5.92]	
Dahl 2000	40.3	23.4	60	43.9	26.4	29	2.3%	-3.60 [-14.89 , 7.69]	
Fiorelli 2015	20.7	0.3	38	24.8	0.3	37	4.5%	-4.10 [-4.24 , -3.96]	
Ganne 2005	40.4	20.6	30	42.5	25.9	31	2.2%	-2.10 [-13.82 , 9.62]	
Garg 2016	2.59	2	22	21.09	12.88	22	3.7%	-18.50 [-23.95 , -13.05]	
Gilabert Morell 2002	17.2	8.6	44	22.6	12.72	22	3.6%	-5.40 [-11.29 , 0.49]	
Guillou 2003	58	35	41	80	37	52	1.7%	-22.00 [-36.69 , -7.31]	
Jaksch 2002	63.47	33.22	15	59.08	57.66	15	0.5%	4.39 [-29.29 , 38.07]	
Kafali 2004	69.8	8	30	86.7	8.4	30	4.0%	-16.90 [-21.05 , -12.75]	
Kamal 2008	66.7	4.94	40	84	9.9	40	4.2%	-17.30 [-20.73 , -13.87]	
Kararmaz 2003	6.06	1.38	20	7.52	2	20	4.5%	-1.46 [-2.52 , -0.40]	
Katz 2004	81	51.6	97	82.1	50.1	46	1.3%	-1.10 [-18.85 , 16.65]	
Kim 2013	61.9	36.6	35	82.6	39	17	1.0%	-20.70 [-42.85 , 1.45]	
Kwon 2009	25.4	6.1	20	29.9	16.2	20	3.2%	-4.50 [-12.09 , 3.09]	
Lahtinen 2004	154.5	66	44	187.5	67.5	46	0.7%	-33.00 [-60.58 , -5.42]	
Lak 2010	3	2	25	17.8	9.2	25	4.1%	-14.80 [-18.49 , -11.11]	
Loftus 2010	195	111	52	309	341	50	0.1%	-114.00 [-213.22 , -14.78]	
Martinez 2014	52	22	28	77	36	32	1.7%	-25.00 [-39.90 , -10.10]	
Menigaux 2000	31.9	22.1	30	67.7	38.3	15	1.0%	-35.80 [-56.73 , -14.87]	
Michelet 2007	41.7	17.9	24	55.8	20.4	24	2.4%	-14.10 [-24.96 , -3.24]	
Papaziogas 2001	0.3	1.15	18	0.9	2.56	17	4.5%	-0.60 [-1.93 , 0.73]	
Remérand 2009	20.7	14.4	79	27	15.3	75	3.9%	-6.30 [-11.00 , -1.60]	
Snijdelaar 2004	47.9	26.2	13	73.4	34.8	12	0.8%	-25.50 [-49.80 , -1.20]	
Snijdelaar 2004	47.93	25.16	13	73.42	33.3	12	0.9%	-25.49 [-48.77 , -2.21]	
Song 2013	77.3	20.2	24	95.7	30.8	25	1.7%	-18.40 [-32.93 , -3.87]	
Subramaniam 2011	202.1	164.3	15	191.2	130.95	15	0.1%	10.90 [-95.42 , 117.22]	
Webb 2007	44.1	41.2	50	72.9	52.7	56	1.3%	-28.80 [-46.71 , -10.89]	
Woo 2014	37.25	3.45	20	42.15	3.3	20	4.4%	-4.90 [-6.99 , -2.81]	
Yalcin 2012	42.52	15.08	26	86.05	29.46	27	2.1%	-43.53 [-56.06 , -31.00]	
Zakine 2008	9.5	10.5	50	12.3	10.7	27	3.8%	-2.80 [-7.78 , 2.18]	
Total (95% CI)			**1342**			**1107**	**100.0%**	**-12.62 [-15.06 , -10.18]**	

Heterogeneity: Tau² = 34.16; Chi² = 701.52, df = 38 (P < 0.00001); I² = 95%
Test for overall effect: Z = 10.14 (P < 0.00001)
Test for subgroup differences: Not applicable



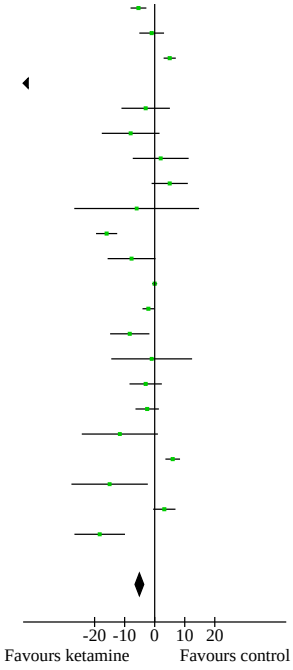
Analysis 1.3. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	28.1	9.4	20	32.5	9.4	20	1.3%	-4.40 [-10.23 , 1.43]
Adriaenssens 1999	25	18	15	36	24	15	0.6%	-11.00 [-26.18 , 4.18]
Argiriadou 2011	22.3	3.4	27	39	10.2	26	1.5%	-16.70 [-20.83 , -12.57]
Arikan 2016	27	5	40	31	10	40	1.5%	-4.00 [-7.46 , -0.54]
Aubrun 2008	15.2	11.8	45	19.3	18.5	45	1.3%	-4.10 [-10.51 , 2.31]
Aveline 2006	32.4	7.8	45	37	7	23	1.5%	-4.60 [-8.26 , -0.94]
Aveline 2009	24	6	25	37	8	24	1.5%	-13.00 [-16.97 , -9.03]
Ayoglu 2005	3.2	1.6	20	4.8	1.6	20	1.7%	-1.60 [-2.59 , -0.61]
Bornemann-Cimenti 2016	17.5	7.2	37	20	9	19	1.4%	-2.50 [-7.16 , 2.16]
Cenzig 2014	2	4.8	30	6.3	6.1	30	1.6%	-4.30 [-7.08 , -1.52]
Chen 2004	29.4	21.4	20	28.9	20.7	20	0.7%	0.50 [-12.55 , 13.55]
Choi 2015	10	5	25	20	15	25	1.3%	-10.00 [-16.20 , -3.80]
D'Alonzo 2011	26	22	20	28	21	20	0.7%	-2.00 [-15.33 , 11.33]
Dahi-Taleghani 2014	10	5	70	17	8	70	1.6%	-7.00 [-9.21 , -4.79]
Dahl 2000	54.5	22	60	58	19	29	1.0%	-3.50 [-12.38 , 5.38]
De Kock 2001	18.8	9.8	40	18	12.3	20	1.3%	0.80 [-5.39 , 6.99]
Dualé 2009	30	27.7	39	32.5	50	41	0.5%	-2.50 [-20.10 , 15.10]
Fiorelli 2015	41	5	38	48	6	37	1.6%	-7.00 [-9.50 , -4.50]
Ganne 2005	16.3	14.9	30	14.2	10.8	31	1.3%	2.10 [-4.45 , 8.65]
Grady 2012	37	22	30	36	17	32	1.0%	1.00 [-8.83 , 10.83]
Guillou 2003	21.8	21.8	41	24.6	18.9	52	1.1%	-2.80 [-11.22 , 5.62]
Hadi 2013	40	7	30	56	5.1	15	1.5%	-16.00 [-19.60 , -12.40]
Haliloglu 2015	4.2	5	26	4.6	5.1	26	1.6%	-0.40 [-3.15 , 2.35]
Hercock 1999	14	12.5	24	12.8	14	25	1.2%	1.20 [-6.22 , 8.62]
Hu 2014	26	12	31	29	12	47	1.4%	-3.00 [-8.44 , 2.44]
Jaksch 2002	10	12	15	14	13	15	1.0%	-4.00 [-12.95 , 4.95]
Javery 1996	23	16.7	22	45	15.4	20	1.0%	-22.00 [-31.71 , -12.29]
Jendoubi 2017	22	6.3	20	31.3	9.4	20	1.4%	-9.30 [-14.26 , -4.34]
Joly 2005	40.7	19.5	24	27.7	16.3	25	0.9%	13.00 [2.92 , 23.08]
Joseph 2012	25	29	22	17.2	17.8	25	0.7%	7.80 [-6.18 , 21.78]
Kafali 2004	11.3	2.7	30	17.1	2.2	30	1.7%	-5.80 [-7.05 , -4.55]
Kakinohana 2004	6	7	25	15	12	25	1.4%	-9.00 [-14.45 , -3.55]
Kamal 2008	26	2.5	40	28.5	4	40	1.7%	-2.50 [-3.96 , -1.04]
Karcioglu 2013	13.5	11.2	17	48	19	20	0.9%	-34.50 [-44.38 , -24.62]
Katz 2004	19.4	2.8	97	16.9	1.9	46	1.7%	2.50 [1.72 , 3.28]
Kim 2013	36.1	16	35	46	23	17	0.8%	-9.90 [-22.05 , 2.25]
Kudoh 2002	13	9	35	25	7	35	1.5%	-12.00 [-15.78 , -8.22]
Kwok 2004	12.4	12.5	90	15.6	8.5	45	1.5%	-3.20 [-6.78 , 0.38]
Kwon 2009	2	7	20	14	8	20	1.4%	-12.00 [-16.66 , -7.34]
Lahtinen 2004	28.5	17.7	44	25.4	20	46	1.1%	3.10 [-4.69 , 10.89]
Lak 2010	32.8	14	25	65.6	13.6	25	1.2%	-32.80 [-40.45 , -25.15]
Leal 2013	15	13	20	5	7	20	1.3%	10.00 [3.53 , 16.47]
Leal 2015	14	15	28	8	10	28	1.2%	6.00 [-0.68 , 12.68]
Lebrun 2006	28.2	6.9	54	35.4	4.2	30	1.6%	-7.20 [-9.58 , -4.82]
Lee 2008	34	9	15	36	13	16	1.1%	-2.00 [-9.83 , 5.83]
Lehmann 2001	11	11	40	11	11	40	1.4%	0.00 [-4.82 , 4.82]
Lin 2016	24	8	30	25	8	29	1.5%	-1.00 [-5.08 , 3.08]
Lo 2008	41	20.2	15	32	17.4	15	0.7%	9.00 [-4.49 , 22.49]
Loftus 2010	47	27	52	48	24	50	0.9%	-1.00 [-10.90 , 8.90]
Mahran 2015	29.3	10.2	30	30	11.4	30	1.4%	-0.70 [-6.17 , 4.77]
Mathisen 1999	20	14	32	24	18	18	1.0%	-4.00 [-13.63 , 5.63]
Mendola 2012	9.72	12.2	32	7.99	9.4	30	1.4%	1.73 [-3.67 , 7.13]
Menigaux 2000	24.7	11.7	30	42.6	19.8	15	0.9%	-17.90 [-28.76 , -7.04]
Menigaux 2001	15.2	12.2	25	26.3	10.1	25	1.3%	-11.10 [-17.31 , -4.89]
Michelet 2007	30	14	24	40	20	24	1.0%	-10.00 [-19.77 , -0.23]
Nesek-Adam 2012	23.3	11.3	20	18.4	11.3	20	1.2%	4.90 [-2.10 , 11.90]
Nielsen 2017	46	19	73	48	20	72	1.3%	-2.00 [-8.35 , 4.35]
Ögün 2001	17	20	16	36	29	15	0.5%	-19.00 [-36.65 , -1.35]
Papaziogas 2001	0	0	18	5	13	17		Not estimable
Parikh 2011	21.4	2.4	30	21.4	9.5	30	1.5%	0.00 [-3.51 , 3.51]
Patel 2016	21	3	25	26.4	6	25	1.6%	-5.40 [-8.03 , -2.77]
Remérand 2009	14	14	79	15	12	75	1.5%	-1.00 [-5.11 , 3.11]
Reza 2010	35	4	30	30	4	30	1.6%	5.00 [2.98 , 7.02]

Analysis 1.3. (Continued)

Patel 2010	21	3	25	20.4	6	25	1.0%	-5.40 [-8.03 , -2.77]
Remérand 2009	14	14	79	15	12	75	1.5%	-1.00 [-5.11 , 3.11]
Reza 2010	35	4	30	30	4	30	1.6%	5.00 [2.98 , 7.02]
Safavi 2011	0.7	1.3	30	59	20	30	1.2%	-58.30 [-65.47 , -51.13]
Sen 2009	10	13	20	13	13	20	1.1%	-3.00 [-11.06 , 5.06]
Snijdelaar 2004	12	10	13	20	14	12	1.0%	-8.00 [-17.61 , 1.61]
Song 2013	25	18	24	23	15	25	1.0%	2.00 [-7.30 , 11.30]
Spreng 2010	14	14	43	9	14	40	1.3%	5.00 [-1.03 , 11.03]
Subramaniam 2011	47	28	15	53	30	15	0.4%	-6.00 [-26.77 , 14.77]
Suzuki 2006	9	4	24	25	8	25	1.5%	-16.00 [-19.52 , -12.48]
Tena 2014	19.4	16.8	33	27.1	16.7	35	1.1%	-7.70 [-15.67 , 0.27]
Ünlügenc 2003	10	1	30	10	2	28	1.7%	0.00 [-0.82 , 0.82]
Van Elstraete 2004	4.2	2	20	6.3	4	20	1.6%	-2.10 [-4.06 , -0.14]
Webb 2007	15.6	16.1	50	23.9	18.4	57	1.3%	-8.30 [-14.84 , -1.76]
Woo 2014	22	21.7	20	23	21.7	20	0.7%	-1.00 [-14.45 , 12.45]
Wu 2009	17	7	15	20	8	15	1.4%	-3.00 [-8.38 , 2.38]
Yalcin 2012	2.5	2.5	26	5	10	27	1.5%	-2.50 [-6.39 , 1.39]
Yamauchi 2008	10.1	15.3	45	21.7	29	23	0.7%	-11.60 [-24.27 , 1.07]
Yazigi 2012	10	3.2	30	4	6	30	1.6%	6.00 [3.57 , 8.43]
Yeom 2012	36	20	20	51	21	20	0.7%	-15.00 [-27.71 , -2.29]
Ysasi 2010	12.9	8.1	30	9.7	6.5	30	1.5%	3.20 [-0.52 , 6.92]
Zakine 2008	16.7	15.9	50	35	19	27	1.1%	-18.30 [-26.71 , -9.89]
Total (95% CI)			**2645**			**2359**	**100.0%**	**-5.09 [-6.55 , -3.64]**

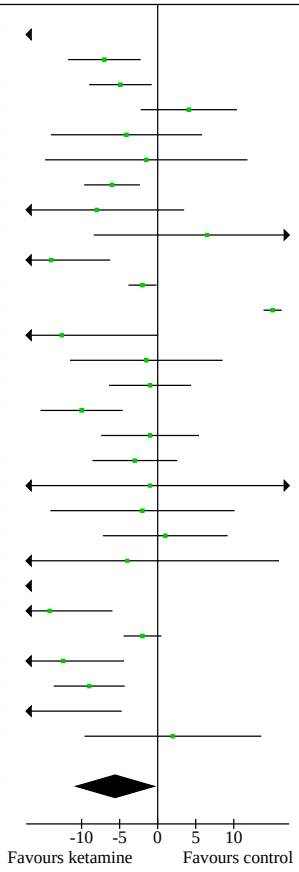
Heterogeneity: Tau² = 32.48; Chi² = 1075.02, df = 80 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.87 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 4: Pain intensity during movement at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	26.5	7.4	27	51.5	8.8	26	3.8%	-25.00 [-29.39 , -20.61]
Aveline 2009	48	9	25	55	8	24	3.7%	-7.00 [-11.76 , -2.24]
Bornemann-Cimenti 2016	30.1	8.2	37	35	7	19	3.8%	-4.90 [-9.01 , -0.79]
De Kock 2001	33	13.2	40	28.9	11	20	3.6%	4.10 [-2.22 , 10.42]
Guillou 2003	37.1	26.8	41	41.2	20.6	52	3.4%	-4.10 [-14.03 , 5.83]
Hercock 1999	41.7	23.2	24	43.2	24.3	25	3.1%	-1.50 [-14.80 , 11.80]
Jendoubi 2017	38	5.9	20	44	5.9	20	3.8%	-6.00 [-9.66 , -2.34]
Joly 2005	36	20	24	44	21	25	3.2%	-8.00 [-19.48 , 3.48]
Joseph 2012	44.8	27.5	20	38.3	21.9	24	2.9%	6.50 [-8.40 , 21.40]
Kakinohana 2004	30	14	25	44	14	25	3.5%	-14.00 [-21.76 , -6.24]
Kamal 2008	38	3.9	40	40	4.5	40	3.8%	-2.00 [-3.85 , -0.15]
Katz 2004	55.7	2.4	97	40.6	3.8	46	3.9%	15.10 [13.90 , 16.30]
Kim 2013	45.4	19.2	35	58	23	17	3.1%	-12.60 [-25.25 , 0.05]
Lahtinen 2004	47.7	23.1	44	49.2	25.4	46	3.4%	-1.50 [-11.52 , 8.52]
Mahran 2015	42.3	10.4	30	43.3	10.9	30	3.7%	-1.00 [-6.39 , 4.39]
Menigaux 2000	48	10	30	58	8	15	3.7%	-10.00 [-15.40 , -4.60]
Nielsen 2017	63	21	72	64	18	70	3.6%	-1.00 [-7.43 , 5.43]
Sen 2009	15	9	20	18	9	20	3.7%	-3.00 [-8.58 , 2.58]
Snijdelaar 2004	27	25	13	28	26	12	2.4%	-1.00 [-21.03 , 19.03]
Song 2013	44	17	24	46	25	24	3.2%	-2.00 [-14.10 , 10.10]
Spreng 2010	16	21	43	15	17	40	3.5%	1.00 [-7.19 , 9.19]
Subramaniam 2011	65	23	15	69	32	15	2.4%	-4.00 [-23.94 , 15.94]
Suzuki 2006	26	5	24	50	7	25	3.8%	-24.00 [-27.40 , -20.60]
Tena 2014	21.5	17.7	33	35.7	17	35	3.5%	-14.20 [-22.46 , -5.94]
Van Elstraete 2004	10	4	20	12	4	20	3.8%	-2.00 [-4.48 , 0.48]
Webb 2007	38.7	22.2	51	51.1	20.2	59	3.5%	-12.40 [-20.38 , -4.42]
Wu 2009	20	6	15	29	7	15	3.7%	-9.00 [-13.67 , -4.33]
Yamauchi 2008	31.1	23.3	45	48.8	27	23	3.1%	-17.70 [-30.67 , -4.73]
Yazigi 2012	26	25.5	30	24	20.1	30	3.2%	2.00 [-9.62 , 13.62]
Total (95% CI)			**964**			**842**	**100.0%**	**-5.60 [-10.72 , -0.48]**

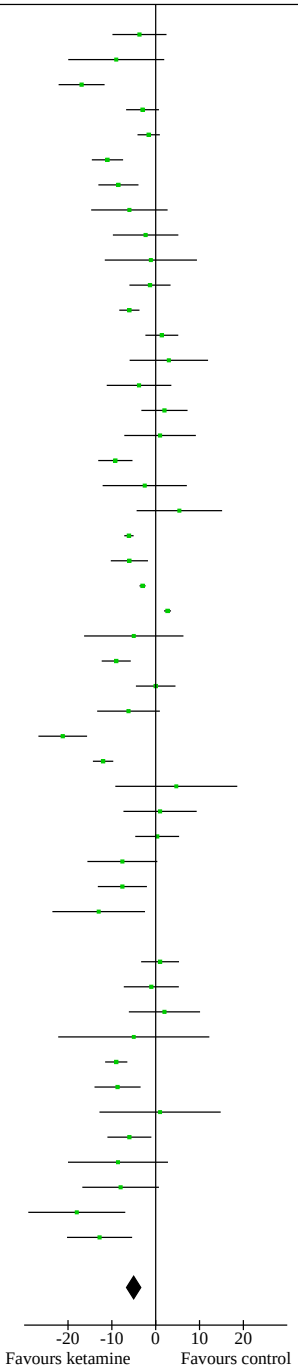
Heterogeneity: Tau² = 176.77; Chi² = 1011.28, df = 28 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 5: Pain intensity at rest at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	16.3	11.9	20	20	7.5	20	2.1%	-3.70 [-9.86 , 2.46]
Adriaenssens 1999	12	12	15	21	18	15	1.3%	-9.00 [-19.95 , 1.95]
Argiriadou 2011	13.6	6.8	27	30.5	11.9	26	2.3%	-16.90 [-22.14 , -11.66]
Arikan 2016	25	11	40	28	5	40	2.7%	-3.00 [-6.74 , 0.74]
Aveline 2006	33.4	5.2	45	35	5	23	2.9%	-1.60 [-4.15 , 0.95]
Aveline 2009	24	4	25	35	8	24	2.7%	-11.00 [-14.56 , -7.44]
Bornemann-Cimenti 2016	10.5	6.6	37	19	9	19	2.5%	-8.50 [-13.07 , -3.93]
Chazan 2010	18	11	24	24	18	22	1.6%	-6.00 [-14.71 , 2.71]
Chen 2004	23.9	14.4	20	26.2	9.1	20	1.9%	-2.30 [-9.77 , 5.17]
Dahl 2000	43.9	23.1	60	45	24	29	1.3%	-1.10 [-11.61 , 9.41]
De Kock 2001	15.1	9	40	16.4	8.6	20	2.5%	-1.30 [-5.99 , 3.39]
Fiorelli 2015	27	6	38	33	4	37	2.9%	-6.00 [-8.30 , -3.70]
Ganne 2005	9.5	6.8	30	8.1	8.1	31	2.7%	1.40 [-2.35 , 5.15]
Grady 2012	31	21	30	28	14	32	1.6%	3.00 [-5.94 , 11.94]
Guillou 2003	15.1	18	41	18.9	18	52	1.9%	-3.80 [-11.17 , 3.57]
Hu 2014	32	12	31	30	11	47	2.3%	2.00 [-3.27 , 7.27]
Jaksch 2002	7	14	15	6	8	15	1.7%	1.00 [-7.16 , 9.16]
Jendoubi 2017	18.8	6.3	20	28	6.3	20	2.6%	-9.20 [-13.10 , -5.30]
Joly 2005	26	13	24	28.5	20.6	25	1.5%	-2.50 [-12.11 , 7.11]
Joseph 2012	18.6	16.3	22	13.2	17.8	25	1.5%	5.40 [-4.35 , 15.15]
Kafali 2004	6	2.1	30	12.1	2.1	30	3.1%	-6.10 [-7.16 , -5.04]
Kakinohana 2004	4	6	25	10	9	25	2.6%	-6.00 [-10.24 , -1.76]
Kamal 2008	19	1	40	22	2	40	3.1%	-3.00 [-3.69 , -2.31]
Katz 2004	14	2.9	97	11.3	1.9	46	3.1%	2.70 [1.90 , 3.50]
Kim 2013	29	18.6	35	34	20	17	1.2%	-5.00 [-16.33 , 6.33]
Kudoh 2002	9	8	35	18	6	35	2.7%	-9.00 [-12.31 , -5.69]
Kwon 2009	2	5	20	2	9	20	2.5%	0.00 [-4.51 , 4.51]
Lahtinen 2004	12.3	16.9	44	18.5	17.7	46	1.9%	-6.20 [-13.35 , 0.95]
Lak 2010	24.8	10.4	25	46	9.6	25	2.3%	-21.20 [-26.75 , -15.65]
Lebrun 2006	23.4	5.2	54	35.4	5.2	30	2.9%	-12.00 [-14.32 , -9.68]
Lo 2008	16.7	22.9	15	12	15.2	15	0.9%	4.70 [-9.21 , 18.61]
Loftus 2010	54	21	52	53	22	50	1.7%	1.00 [-7.35 , 9.35]
Mendola 2012	6.42	11.3	32	6.08	8.7	30	2.4%	0.34 [-4.66 , 5.34]
Menigaux 2000	16.7	12.8	30	24.3	12.9	15	1.8%	-7.60 [-15.57 , 0.37]
Menigaux 2001	8.1	10.1	25	15.7	10.1	25	2.3%	-7.60 [-13.20 , -2.00]
Michelet 2007	29	16	24	42	21	24	1.3%	-13.00 [-23.56 , -2.44]
Papaziogas 2001	0	0	18	5	13	17		Not estimable
Remérand 2009	15	16	79	14	11	75	2.5%	1.00 [-3.32 , 5.32]
Snijdelaar 2004	8	8	13	9	8	12	2.1%	-1.00 [-7.28 , 5.28]
Song 2013	22	14	24	20	15	25	1.7%	2.00 [-6.12 , 10.12]
Subramaniam 2011	43	22	15	48	26	15	0.7%	-5.00 [-22.24 , 12.24]
Suzuki 2006	9	4	24	18	5	25	2.9%	-9.00 [-11.53 , -6.47]
Webb 2007	9.7	10.3	51	18.4	16.3	52	2.3%	-8.70 [-13.96 , -3.44]
Woo 2014	23	22.9	20	22	21.7	20	1.0%	1.00 [-12.83 , 14.83]
Wu 2009	15	7	15	21	7	15	2.4%	-6.00 [-11.01 , -0.99]
Yamauchi 2008	7.1	19.9	45	15.7	24	23	1.2%	-8.60 [-20.00 , 2.80]
Yazigi 2012	9	14	30	17	20	30	1.6%	-8.00 [-16.74 , 0.74]
Yeom 2012	24	14	20	42	21	20	1.3%	-18.00 [-29.06 , -6.94]
Zakine 2008	12.2	13.5	50	25	17	27	1.9%	-12.80 [-20.22 , -5.38]
Total (95% CI)			**1591**			**1371**	**100.0%**	**-5.03 [-6.65 , -3.40]**

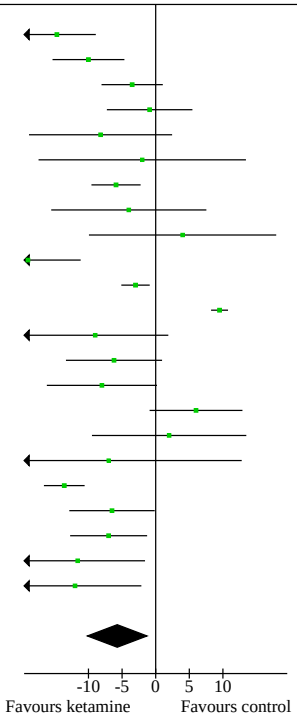
Heterogeneity: Tau² = 22.21; Chi² = 491.41, df = 47 (P < 0.00001); I² = 90%
Test for overall effect: Z = 6.07 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 6: Pain intensity during movement at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	20.6	7.4	27	35.3	13.2	26	4.8%	-14.70 [-20.49 , -8.91]
Aveline 2009	49	6	25	59	12	24	4.8%	-10.00 [-15.35 , -4.65]
Bornemann-Cimenti 2016	27.5	6.5	37	31	9	19	4.9%	-3.50 [-8.06 , 1.06]
De Kock 2001	28	13.4	40	28.9	11	20	4.7%	-0.90 [-7.26 , 5.46]
Guillou 2003	26.8	26.8	41	35	24.7	51	4.0%	-8.20 [-18.84 , 2.44]
Jaksch 2002	21	20	15	23	23	15	3.2%	-2.00 [-17.42 , 13.42]
Jendoubi 2017	35.3	5.9	20	41.2	5.9	20	5.0%	-5.90 [-9.56 , -2.24]
Joly 2005	33	18	24	37	23	25	3.8%	-4.00 [-15.54 , 7.54]
Joseph 2012	38.2	18.3	22	34.2	29.1	24	3.4%	4.00 [-9.93 , 17.93]
Kakinohana 2004	23	12	25	42	16	25	4.5%	-19.00 [-26.84 , -11.16]
Kamal 2008	32	4.49	40	35	5.13	40	5.1%	-3.00 [-5.11 , -0.89]
Katz 2004	47.2	3.1	97	37.7	3.8	46	5.2%	9.50 [8.24 , 10.76]
Kim 2013	36	18.3	35	45	19	17	3.9%	-9.00 [-19.88 , 1.88]
Lahtinen 2004	12.3	16.9	44	18.5	17.7	46	4.6%	-6.20 [-13.35 , 0.95]
Menigaux 2000	28	18	30	36	10	15	4.4%	-8.00 [-16.19 , 0.19]
Snijdelaar 2004	11	12	13	5	4	12	4.6%	6.00 [-0.90 , 12.90]
Song 2013	42	20	24	40	21	25	3.8%	2.00 [-9.48 , 13.48]
Subramaniam 2011	63	21	15	70	33	15	2.5%	-7.00 [-26.79 , 12.79]
Suzuki 2006	29	3.4	24	42.6	6.9	25	5.1%	-13.60 [-16.63 , -10.57]
Webb 2007	32.9	16.4	51	39.4	17.1	56	4.7%	-6.50 [-12.85 , -0.15]
Wu 2009	18	8	15	25	8	15	4.8%	-7.00 [-12.73 , -1.27]
Yamauchi 2008	26.2	19.8	45	37.8	20	23	4.1%	-11.60 [-21.61 , -1.59]
Yazigi 2012	32	19.5	30	44	19.5	30	4.1%	-12.00 [-21.87 , -2.13]
Total (95% CI)			**739**			**614**	**100.0%**	**-5.72 [-10.15 , -1.29]**

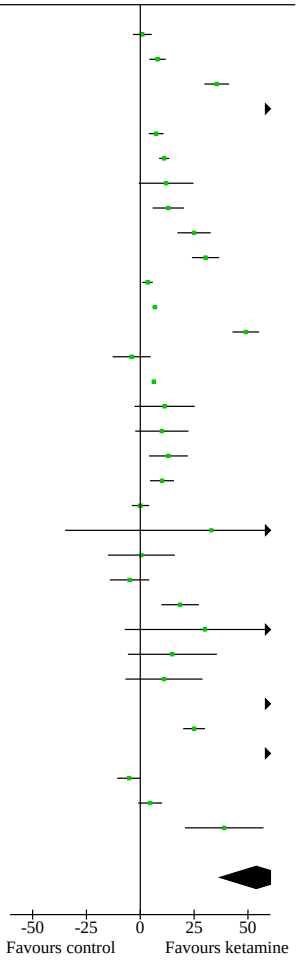
Heterogeneity: Tau² = 98.70; Chi² = 409.22, df = 22 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 7: Time to first request for analgesia/trigger of PCA

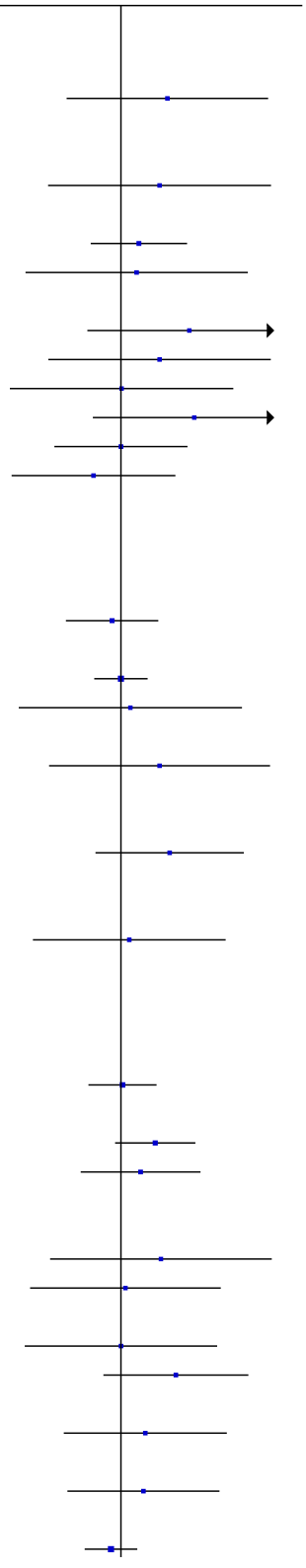
Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	10	7	20	9	7	20	3.1%	1.00 [-3.34 , 5.34]
Aqil 2011	25	6.9	30	17	5.7	15	3.1%	8.00 [4.20 , 11.80]
Aqil 2011	52.5	19.5	60	17	5.7	15	3.1%	35.50 [29.78 , 41.22]
Ataskhoyi 2013	165	28	30	17	8.5	30	3.1%	148.00 [137.53 , 158.47]
Aveline 2009	52.3	7.2	25	44.9	4.6	24	3.1%	7.40 [4.03 , 10.77]
Cenzig 2014	22.7	5.7	30	11.6	3.2	30	3.1%	11.10 [8.76 , 13.44]
Choi 2015	51.6	26.7	25	39.6	18.4	25	3.0%	12.00 [-0.71 , 24.71]
Dal 2005	25	18	30	12	9.5	30	3.1%	13.00 [5.72 , 20.28]
Dar 2012	70	18	30	45	12	30	3.1%	25.00 [17.26 , 32.74]
Gilabert Morell 2002	35.8	16.9	44	5.5	9.2	22	3.1%	30.30 [24.00 , 36.60]
Hadi 2010	22.9	3.5	15	19.5	3.2	15	3.1%	3.40 [1.00 , 5.80]
Hadi 2013	23.8	1.8	30	17	1.7	15	3.1%	6.80 [5.73 , 7.87]
Helmy 2015	82	12	19	33	7	20	3.1%	49.00 [42.79 , 55.21]
Jaksch 2002	10	7	15	14	16	15	3.1%	-4.00 [-12.84 , 4.84]
Kafali 2004	17.7	2.2	30	11.4	1.2	30	3.1%	6.30 [5.40 , 7.20]
Kakinohana 2004	60.5	28	25	49.2	22.2	25	3.0%	11.30 [-2.71 , 25.31]
Karaman 2006	44.5	28	40	34.5	20.1	20	3.1%	10.00 [-2.36 , 22.36]
Kararmaz 2003	22.3	17.1	20	9.2	11.5	20	3.1%	13.10 [4.07 , 22.13]
Köse 2012	27.3	11.5	30	17.2	7.4	15	3.1%	10.10 [4.54 , 15.66]
Köse 2012	17.3	5.9	60	17.2	7.4	15	3.1%	0.10 [-3.93 , 4.13]
Lahtinen 2004	134	125	44	101	197	46	2.1%	33.00 [-34.86 , 100.86]
Leal 2013	22	24.9	20	21.5	28.1	25	3.0%	0.50 [-15.01 , 16.01]
Lin 2016	113	14	30	118	21	29	3.1%	-5.00 [-14.14 , 4.14]
Menigaux 2000	28.5	22.2	30	10	7	15	3.1%	18.50 [9.80 , 27.20]
Nesek-Adam 2012	108	60	20	78	60	20	2.7%	30.00 [-7.19 , 67.19]
Ong 2001	42.8	46.9	20	27.9	4.6	20	3.0%	14.90 [-5.75 , 35.55]
Papaziogas 2001	132	34	18	121	18	17	3.0%	11.00 [-6.89 , 28.89]
Parikh 2011	1296	7.2	30	228	42	30	3.0%	1068.00 [1052.75 , 1083.25]
Roytblat 1993	35	5	11	10	7	11	3.1%	25.00 [19.92 , 30.08]
Safavi 2011	170	17.3	30	17.5	5.7	30	3.1%	152.50 [145.98 , 159.02]
Sahin 2004	5.5	3.3	17	10.7	10.8	16	3.1%	-5.20 [-10.72 , 0.32]
Song 2014	36.8	9.7	25	32.2	10.3	25	3.1%	4.60 [-0.95 , 10.15]
Ysasi 2010	102	38	30	63	34	30	3.0%	39.00 [20.75 , 57.25]
Total (95% CI)			**933**			**745**	**100.0%**	**53.89 [37.00 , 70.78]**

Heterogeneity: Tau² = 2391.59; Chi² = 21551.52, df = 32 (P < 0.00001); I² = 100%
Test for overall effect: Z = 6.26 (P < 0.00001)
Test for subgroup differences: Not applicable



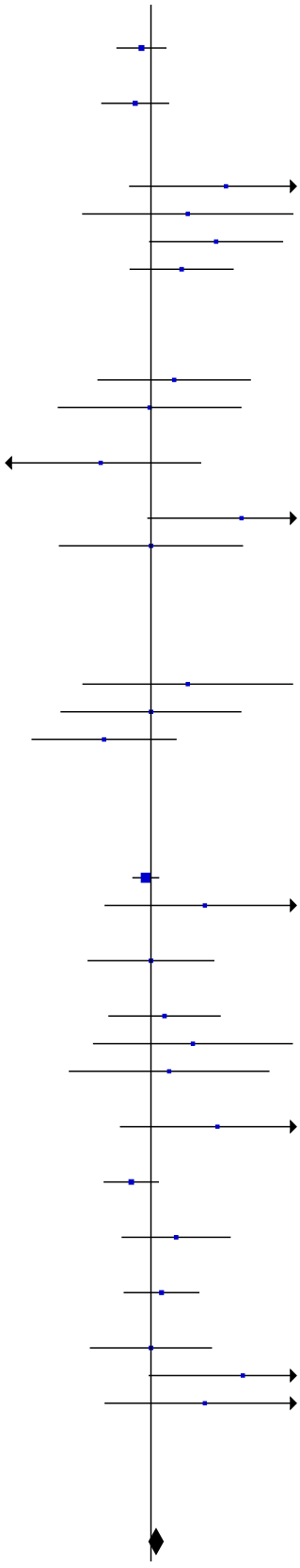
Analysis 1.8. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 8: CNS adverse events - all studies

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Adam 2005	0	20	0	20		Not estimable
Adriaenssens 1999	0	15	0	15		Not estimable
Aqil 2011	5	90	0	30	0.5%	3.75 [0.21 , 65.84]
Argiriadou 2004	0	30	0	15		Not estimable
Argiriadou 2011	0	27	0	26		Not estimable
Arikan 2016	1	40	0	40	0.4%	3.00 [0.13 , 71.51]
Ataskhoyi 2013	0	30	0	30		Not estimable
Aubrun 2008	5	45	3	45	2.3%	1.67 [0.42 , 6.56]
Aveline 2006	1	45	0	23	0.4%	1.57 [0.07 , 36.98]
Aveline 2009	0	25	0	24		Not estimable
Ayoglu 2005	3	20	0	20	0.5%	7.00 [0.38 , 127.32]
Barreveld 2013	1	32	0	32	0.4%	3.00 [0.13 , 71.00]
Bilgen 2012	1	105	0	35	0.4%	1.02 [0.04 , 24.46]
Burstal 2001	4	37	0	33	0.5%	8.05 [0.45 , 144.15]
Cenzig 2014	2	30	2	30	1.2%	1.00 [0.15 , 6.64]
Chazan 2010	1	24	2	22	0.8%	0.46 [0.04 , 4.71]
Chen 2004	0	20	0	20		Not estimable
D'Alonzo 2011	0	20	0	20		Not estimable
Dal 2005	0	30	0	30		Not estimable
De Kock 2001	0	40	0	20		Not estimable
Deng 2009	7	150	3	50	2.5%	0.78 [0.21 , 2.89]
Du 2011	0	20	0	20		Not estimable
Dualé 2009	8	20	8	20	7.5%	1.00 [0.47 , 2.14]
Dullenkopf 2009	1	77	0	33	0.4%	1.31 [0.05 , 31.29]
Fiorelli 2015	0	38	0	37		Not estimable
Galinski 2007	1	20	0	20	0.4%	3.00 [0.13 , 69.52]
Ganne 2005	0	30	0	31		Not estimable
Garcia-Navia 2016	0	11	0	11		Not estimable
Garg 2016	4	22	1	22	1.0%	4.00 [0.48 , 33.00]
Gilabert Morell 2002	0	22	0	22		Not estimable
Guignard 2002	0	25	0	25		Not estimable
Guillou 2003	1	41	1	52	0.6%	1.27 [0.08 , 19.67]
Hadi 2010	0	15	0	15		Not estimable
Hadi 2013	0	15	0	15		Not estimable
Haliloglu 2015	0	26	0	26		Not estimable
Hasanein 2011	0	30	0	30		Not estimable
Hayes 2004	6	22	6	23	4.6%	1.05 [0.40 , 2.75]
Hercock 1999	0	24	0	25		Not estimable
Hu 2014	7	31	4	47	3.3%	2.65 [0.85 , 8.31]
Ilkjaer 1998	3	24	2	28	1.5%	1.75 [0.32 , 9.62]
Jaksch 2002	0	15	0	15		Not estimable
Jendoubi 2017	0	20	0	20		Not estimable
Joly 2005	1	24	0	25	0.4%	3.12 [0.13 , 73.04]
Joseph 2012	1	22	1	25	0.6%	1.14 [0.08 , 17.11]
Kafali 2004	0	30	0	30		Not estimable
Kamal 2008	1	40	1	40	0.6%	1.00 [0.06 , 15.44]
Kapfer 2005	5	22	1	21	1.0%	4.77 [0.61 , 37.52]
Karaman 2006	0	40	0	20		Not estimable
Kararmaz 2003	2	20	1	20	0.8%	2.00 [0.20 , 20.33]
Karcioglu 2013	0	17	0	20		Not estimable
Katz 2004	4	97	1	46	0.9%	1.90 [0.22 , 16.50]
Kim 2013	0	35	0	17		Not estimable
Kim 2016	8	28	11	29	7.8%	0.75 [0.36 , 1.59]



Analysis 1.8. (Continued)

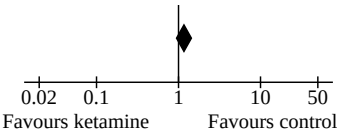
Kim 2013	0	35	0	17		Not estimable
Kim 2016	8	28	11	29	7.8%	0.75 [0.36 , 1.59]
Köse 2012	0	90	0	30		Not estimable
Kudoh 2002	5	35	8	35	4.2%	0.63 [0.23 , 1.72]
Kwok 2004	0	90	0	45		Not estimable
Kwon 2009	0	20	0	20		Not estimable
Lahtinen 2004	4	44	0	46	0.5%	9.40 [0.52 , 169.65]
Lak 2010	1	25	0	25	0.4%	3.00 [0.13 , 70.30]
Leal 2013	7	20	1	20	1.1%	7.00 [0.95 , 51.80]
Leal 2015	5	28	2	28	1.8%	2.50 [0.53 , 11.82]
Lebrun 2006	0	54	0	30		Not estimable
Lehmann 2001	0	40	0	40		Not estimable
Lin 2016	0	30	0	29		Not estimable
Lo 2008	2	15	1	15	0.8%	2.00 [0.20 , 19.78]
Loftus 2010	1	52	1	50	0.6%	0.96 [0.06 , 14.96]
Mahran 2015	0	30	0	30		Not estimable
Martinez 2014	0	34	2	38	0.5%	0.22 [0.01 , 4.48]
Mathisen 1999	0	40	0	20		Not estimable
McKay 2007	6	19	0	22	0.5%	14.95 [0.90 , 249.15]
Mebazaa MS 2008	1	67	1	67	0.6%	1.00 [0.06 , 15.66]
Mendola 2012	0	32	0	30		Not estimable
Menigaux 2000	0	30	0	15		Not estimable
Menigaux 2001	0	25	0	25		Not estimable
Michelet 2007	0	24	0	24		Not estimable
Miziara 2016	1	21	0	21	0.4%	3.00 [0.13 , 69.70]
Nesek-Adam 2012	1	20	1	20	0.6%	1.00 [0.07 , 14.90]
Nielsen 2017	1	74	4	73	0.9%	0.25 [0.03 , 2.15]
Pacreu 2012	0	10	0	10		Not estimable
Papaziogas 2001	0	18	0	17		Not estimable
Parikh 2011	0	30	0	30		Not estimable
Pirim 2006	0	23	0	22		Not estimable
Remérand 2009	28	79	31	75	26.9%	0.86 [0.57 , 1.28]
Reza 2010	2	30	0	30	0.5%	5.00 [0.25 , 99.95]
Roytblat 1993	0	11	0	11		Not estimable
Safavi 2011	2	30	2	30	1.2%	1.00 [0.15 , 6.64]
Sahin 2004	0	17	0	16		Not estimable
Sen 2009	3	20	2	20	1.5%	1.50 [0.28 , 8.04]
Siddiqui 2015	2	29	0	20	0.5%	3.50 [0.18 , 69.23]
Singh 2013	2	60	0	20	0.5%	1.72 [0.09 , 34.42]
Snijdelaar 2004	0	13	0	12		Not estimable
Song 2013	3	24	0	25	0.5%	7.28 [0.40 , 133.89]
Spreng 2010	0	43	0	40		Not estimable
Subramaniam 2011	5	15	9	15	6.4%	0.56 [0.24 , 1.27]
Suzuki 1999	0	105	0	35		Not estimable
Tena 2014	4	33	2	35	1.6%	2.12 [0.42 , 10.82]
Van Elstraete 2004	0	20	0	20		Not estimable
Webb 2007	6	56	5	64	3.4%	1.37 [0.44 , 4.25]
Woo 2014	0	20	0	20		Not estimable
Wu 2009	2	15	2	15	1.3%	1.00 [0.16 , 6.20]
Yalcin 2012	7	26	0	27	0.5%	15.56 [0.93 , 259.28]
Yazigi 2012	2	30	0	30	0.5%	5.00 [0.25 , 99.95]
Yeom 2012	0	20	0	20		Not estimable
Ysasi 2010	0	30	0	30		Not estimable
Zakine 2008	0	50	0	27		Not estimable
Total (95% CI)		**3614**		**2924**	**100.0%**	**1.17 [0.95 , 1.43]**



Analysis 1.8. (Continued)

Total (95% CI)	**3614**	**2924**	**100.0%**	**1.17 [0.95 , 1.43]**	
Total events:	187	122			

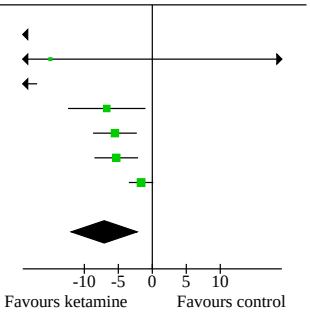
Heterogeneity: Tau² = 0.00; Chi² = 44.83, df = 51 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 9: Hyperalgesia

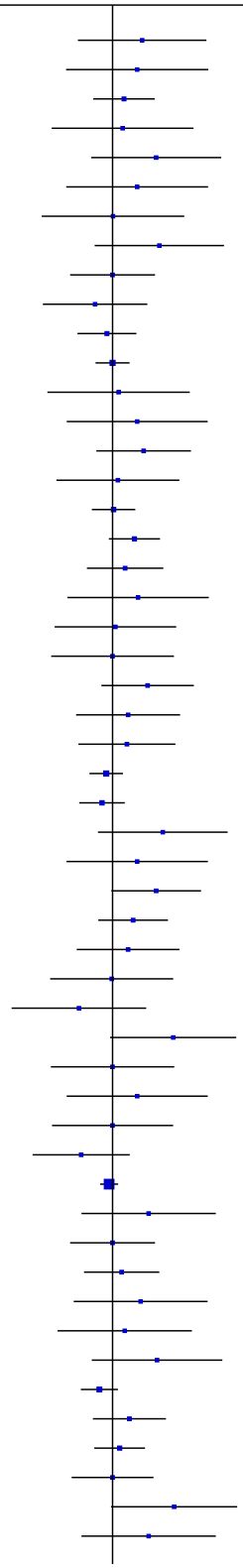
Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Stubhaug 1997	66.68	45.75	10	218.2	114.2	10	0.4%	-151.52 [-227.77 , -75.27]
Burstal 2001	42	57	24	57	82	18	1.1%	-15.00 [-59.22 , 29.22]
De Kock 2001	5.8	24.7	40	40.6	36.8	20	5.8%	-34.80 [-52.65 , -16.95]
Bornemann-Cimenti 2016	4.9	4.7	37	11.6	12.2	19	19.4%	-6.70 [-12.39 , -1.01]
Song 2014	10.2	5.8	25	15.7	5.8	25	23.8%	-5.50 [-8.72 , -2.28]
Joly 2005	8.4	4	24	13.7	7.1	25	23.8%	-5.30 [-8.51 , -2.09]
Leal 2015	7.08	4.65	28	8.73	1.35	28	25.6%	-1.65 [-3.44 , 0.14]
Total (95% CI)			**188**			**145**	**100.0%**	**-7.08 [-11.92 , -2.23]**

Heterogeneity: Tau² = 22.96; Chi² = 34.54, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 10: CNS adverse events - studies with events

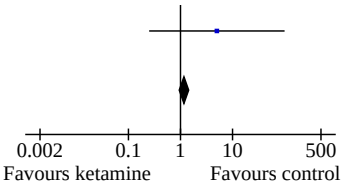
Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Aqil 2011	5	90	0	30	0.5%	3.75 [0.21 , 65.84]
Arikan 2016	1	40	0	40	0.4%	3.00 [0.13 , 71.51]
Aubrun 2008	5	45	3	45	2.3%	1.67 [0.42 , 6.56]
Aveline 2006	1	45	0	23	0.4%	1.57 [0.07 , 36.98]
Ayoglu 2005	3	20	0	20	0.5%	7.00 [0.38 , 127.32]
Barreveld 2013	1	32	0	32	0.4%	3.00 [0.13 , 71.00]
Bilgen 2012	1	105	0	35	0.4%	1.02 [0.04 , 24.46]
Burstal 2001	4	37	0	33	0.5%	8.05 [0.45 , 144.15]
Cenzig 2014	2	30	2	30	1.2%	1.00 [0.15 , 6.64]
Chazan 2010	1	24	2	22	0.8%	0.46 [0.04 , 4.71]
Deng 2009	7	150	3	50	2.5%	0.78 [0.21 , 2.89]
Dualé 2009	8	20	8	20	7.5%	1.00 [0.47 , 2.14]
Dullenkopf 2009	1	77	0	33	0.4%	1.31 [0.05 , 31.29]
Galinski 2007	1	20	0	20	0.4%	3.00 [0.13 , 69.52]
Garg 2016	4	22	1	22	1.0%	4.00 [0.48 , 33.00]
Guillou 2003	1	41	1	52	0.6%	1.27 [0.08 , 19.67]
Hayes 2004	6	22	6	23	4.6%	1.05 [0.40 , 2.75]
Hu 2014	7	31	4	47	3.3%	2.65 [0.85 , 8.31]
Ilkjaer 1998	3	24	2	28	1.5%	1.75 [0.32 , 9.62]
Joly 2005	1	24	0	25	0.4%	3.12 [0.13 , 73.04]
Joseph 2012	1	22	1	25	0.6%	1.14 [0.08 , 17.11]
Kamal 2008	1	40	1	40	0.6%	1.00 [0.06 , 15.44]
Kapfer 2005	5	22	1	21	1.0%	4.77 [0.61 , 37.52]
Kararmaz 2003	2	20	1	20	0.8%	2.00 [0.20 , 20.33]
Katz 2004	4	97	1	46	0.9%	1.90 [0.22 , 16.50]
Kim 2016	8	28	11	29	7.8%	0.75 [0.36 , 1.59]
Kudoh 2002	5	35	8	35	4.2%	0.63 [0.23 , 1.72]
Lahtinen 2004	4	44	0	46	0.5%	9.40 [0.52 , 169.65]
Lak 2010	1	25	0	25	0.4%	3.00 [0.13 , 70.30]
Leal 2013	7	20	1	20	1.1%	7.00 [0.95 , 51.80]
Leal 2015	5	28	2	28	1.8%	2.50 [0.53 , 11.82]
Lo 2008	2	15	1	15	0.8%	2.00 [0.20 , 19.78]
Loftus 2010	1	52	1	50	0.6%	0.96 [0.06 , 14.96]
Martinez 2014	0	34	2	38	0.5%	0.22 [0.01 , 4.48]
McKay 2007	6	19	0	22	0.5%	14.95 [0.90 , 249.15]
Mebazaa MS 2008	1	67	1	67	0.6%	1.00 [0.06 , 15.66]
Miziara 2016	1	21	0	21	0.4%	3.00 [0.13 , 69.70]
Nesek-Adam 2012	1	20	1	20	0.6%	1.00 [0.07 , 14.90]
Nielsen 2017	1	74	4	73	0.9%	0.25 [0.03 , 2.15]
Remérand 2009	28	79	31	75	26.9%	0.86 [0.57 , 1.28]
Reza 2010	2	30	0	30	0.5%	5.00 [0.25 , 99.95]
Safavi 2011	2	30	2	30	1.2%	1.00 [0.15 , 6.64]
Sen 2009	3	20	2	20	1.5%	1.50 [0.28 , 8.04]
Siddiqui 2015	2	29	0	20	0.5%	3.50 [0.18 , 69.23]
Singh 2013	2	60	0	20	0.5%	1.72 [0.09 , 34.42]
Song 2013	3	24	0	25	0.5%	7.28 [0.40 , 133.89]
Subramaniam 2011	5	15	9	15	6.4%	0.56 [0.24 , 1.27]
Tena 2014	4	33	2	35	1.6%	2.12 [0.42 , 10.82]
Webb 2007	6	56	5	64	3.4%	1.37 [0.44 , 4.25]
Wu 2009	2	15	2	15	1.3%	1.00 [0.16 , 6.20]
Yalcin 2012	7	26	0	27	0.5%	15.56 [0.93 , 259.28]
Yazigi 2012	2	30	0	30	0.5%	5.00 [0.25 , 99.95]



Analysis 1.10. (Continued)

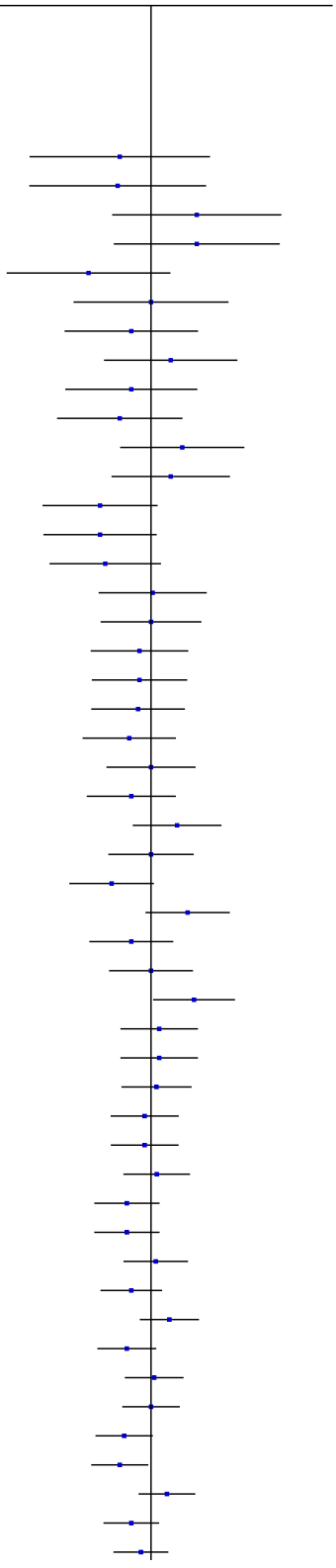
Yazigi 2012	2	30	0	30	0.5%	5.00 [0.25 , 99.95]
Total (95% CI)		**2029**		**1677**	**100.0%**	**1.17 [0.95 , 1.43]**
Total events:	187		122			

Heterogeneity: Tau² = 0.00; Chi² = 44.83, df = 51 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Perioperative ketamine versus control in a non-stratified study population, Outcome 11: Postoperative nausea and vomiting - all studies

Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Galinski 2007	0	20	0	20		Not estimable
Helmy 2015	0	20	0	30		Not estimable
Menigaux 2001	0	25	0	25		Not estimable
Fiorelli 2015	0	38	0	37		Not estimable
Abdolahi 2013	0	44	1	44	0.1%	0.33 [0.01 , 7.97]
Snijdelaar 2004	0	13	1	12	0.1%	0.31 [0.01 , 6.94]
Woo 2014	2	20	0	20	0.1%	5.00 [0.26 , 98.00]
Pacreu 2012	2	10	0	10	0.1%	5.00 [0.27 , 92.62]
Parikh 2011	0	30	4	30	0.1%	0.11 [0.01 , 1.98]
Dar 2012	1	30	1	30	0.1%	1.00 [0.07 , 15.26]
Kafali 2004	1	30	2	30	0.1%	0.50 [0.05 , 5.22]
Safavi 2011	2	30	1	30	0.1%	2.00 [0.19 , 20.90]
Miziara 2016	1	21	2	21	0.1%	0.50 [0.05 , 5.10]
Dal 2005	1	30	3	30	0.1%	0.33 [0.04 , 3.03]
Garg 2016	3	22	1	22	0.2%	3.00 [0.34 , 26.66]
Bilgen 2012	6	105	1	35	0.2%	2.00 [0.25 , 16.04]
Kararmaz 2003	1	20	6	20	0.2%	0.17 [0.02 , 1.26]
Adriaenssens 1999	1	15	6	15	0.2%	0.17 [0.02 , 1.22]
Stubhaug 1997	1	10	5	10	0.2%	0.20 [0.03 , 1.42]
Tena 2014	2	33	2	35	0.2%	1.06 [0.16 , 7.10]
Roytblat 1993	2	11	2	11	0.2%	1.00 [0.17 , 5.89]
Hasanein 2011	2	30	3	30	0.2%	0.67 [0.12 , 3.71]
Kwon 2009	2	20	3	20	0.3%	0.67 [0.12 , 3.57]
Guillou 2003	2	41	4	52	0.3%	0.63 [0.12 , 3.29]
Spreng 2010	2	43	4	40	0.3%	0.47 [0.09 , 2.40]
Deng 2009	6	150	2	50	0.3%	1.00 [0.21 , 4.80]
Crousier 2008	2	18	4	18	0.3%	0.50 [0.10 , 2.40]
Ataskhoyi 2013	5	30	2	30	0.3%	2.50 [0.53 , 11.89]
Lak 2010	3	25	3	25	0.3%	1.00 [0.22 , 4.49]
Kamal 2008	2	40	8	40	0.3%	0.25 [0.06 , 1.11]
Kim 2016	7	28	2	29	0.3%	3.63 [0.82 , 15.98]
Menigaux 2000	3	30	3	15	0.3%	0.50 [0.11 , 2.19]
Yeom 2012	3	20	3	20	0.3%	1.00 [0.23 , 4.37]
Joseph 2012	8	22	2	25	0.3%	4.55 [1.08 , 19.18]
Nesek-Adam 2012	4	20	3	20	0.4%	1.33 [0.34 , 5.21]
Van Elstraete 2004	4	20	3	20	0.4%	1.33 [0.34 , 5.21]
Hu 2014	4	31	5	47	0.5%	1.21 [0.35 , 4.17]
Haliloglu 2015	4	26	5	26	0.5%	0.80 [0.24 , 2.65]
Guignard 2002	4	25	5	25	0.5%	0.80 [0.24 , 2.64]
Singh 2013	11	60	3	20	0.5%	1.22 [0.38 , 3.95]
Subramaniam 2011	3	15	7	15	0.5%	0.43 [0.14 , 1.35]
Wu 2009	3	15	7	15	0.5%	0.43 [0.14 , 1.35]
Papaziogas 2001	5	18	4	17	0.5%	1.18 [0.38 , 3.67]
Siddiqui 2015	4	29	8	29	0.6%	0.50 [0.17 , 1.48]
Kapfer 2005	8	22	4	21	0.6%	1.91 [0.67 , 5.40]
Aveline 2009	4	25	9	24	0.7%	0.43 [0.15 , 1.20]
Martinez 2014	6	34	6	38	0.7%	1.12 [0.40 , 3.14]
Mahran 2015	6	30	6	30	0.7%	1.00 [0.36 , 2.75]
Köse 2012	7	90	6	30	0.7%	0.39 [0.14 , 1.07]
Garcia-Navia 2016	3	11	9	11	0.7%	0.33 [0.12 , 0.91]
Jaksch 2002	7	15	4	15	0.7%	1.75 [0.64 , 4.75]
Arikan 2016	5	40	10	40	0.7%	0.50 [0.19 , 1.33]
Argiriadou 2004	7	30	5	15	0.7%	0.70 [0.27 , 1.84]



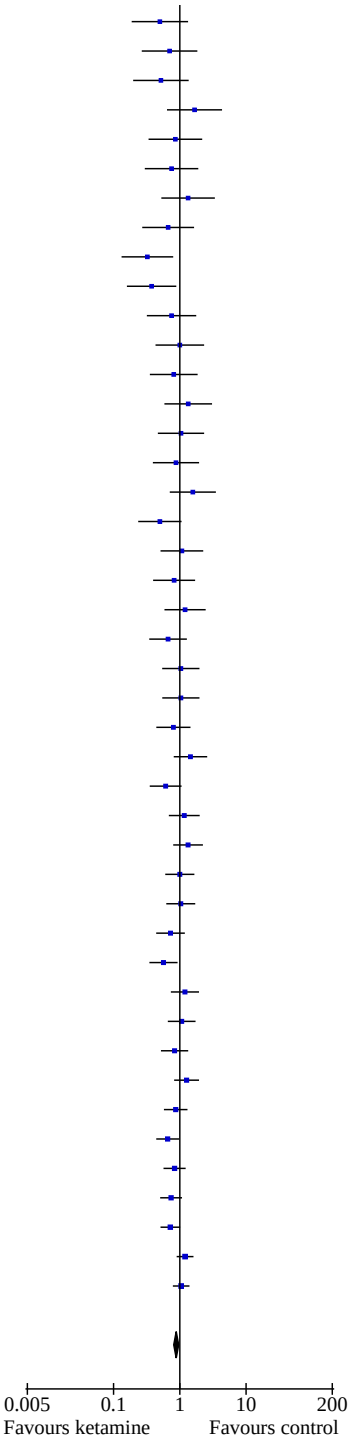
Analysis 1.11. (Continued)

Arikan 2016	5	40	10	40	0.7%	0.50 [0.19 , 1.33]
Argiriadou 2004	7	30	5	15	0.7%	0.70 [0.27 , 1.84]
Ünlügenc 2003	5	30	9	28	0.7%	0.52 [0.20 , 1.36]
Dahi-Taleghani 2014	10	70	6	70	0.8%	1.67 [0.64 , 4.34]
Michelet 2007	6	24	7	24	0.8%	0.86 [0.34 , 2.18]
Reza 2010	6	30	8	30	0.8%	0.75 [0.30 , 1.90]
Yazigi 2012	8	30	6	30	0.8%	1.33 [0.53 , 3.38]
Ysasi 2010	6	30	9	30	0.9%	0.67 [0.27 , 1.64]
Zakine 2008	6	50	10	27	0.9%	0.32 [0.13 , 0.79]
Hadi 2013	6	30	8	15	0.9%	0.38 [0.16 , 0.88]
Ayoglu 2005	6	20	8	20	0.9%	0.75 [0.32 , 1.77]
Ong 2001	7	20	7	20	1.0%	1.00 [0.43 , 2.33]
Kim 2013	10	35	6	17	1.0%	0.81 [0.35 , 1.86]
Mendola 2012	10	32	7	30	1.0%	1.34 [0.59 , 3.06]
Joly 2005	8	24	8	25	1.0%	1.04 [0.47 , 2.33]
Sen 2009	7	20	8	20	1.1%	0.88 [0.39 , 1.95]
Ozhan 2013	11	30	7	30	1.1%	1.57 [0.71 , 3.50]
Cenzig 2014	7	30	14	30	1.2%	0.50 [0.24 , 1.06]
Lin 2016	10	30	9	29	1.2%	1.07 [0.51 , 2.26]
Ögün 2001	7	16	8	15	1.3%	0.82 [0.40 , 1.70]
Lehmann 2001	12	40	10	40	1.3%	1.20 [0.59 , 2.45]
Aveline 2006	13	45	10	23	1.5%	0.66 [0.35 , 1.28]
Loftus 2010	14	52	13	50	1.6%	1.04 [0.54 , 1.98]
Suzuki 1999	28	105	9	35	1.6%	1.04 [0.54 , 1.98]
Lo 2008	8	15	10	15	1.8%	0.80 [0.44 , 1.45]
Lahtinen 2004	18	44	13	46	1.9%	1.45 [0.81 , 2.59]
Chazan 2010	10	24	15	22	2.0%	0.61 [0.35 , 1.06]
Kakinohana 2004	14	25	12	25	2.1%	1.17 [0.68 , 1.99]
Dualé 2009	19	39	15	41	2.3%	1.33 [0.79 , 2.23]
Kwok 2004	30	90	15	45	2.4%	1.00 [0.60 , 1.66]
Nielsen 2017	22	74	21	73	2.4%	1.03 [0.62 , 1.71]
McKay 2007	10	19	16	22	2.4%	0.72 [0.44 , 1.19]
Mebazaa MS 2008	17	67	30	67	2.5%	0.57 [0.35 , 0.92]
Aqil 2011	43	90	12	30	2.5%	1.19 [0.73 , 1.95]
Grady 2012	16	30	16	32	2.6%	1.07 [0.66 , 1.73]
Karaman 2006	20	40	12	20	2.6%	0.83 [0.52 , 1.34]
Song 2013	17	24	14	25	3.0%	1.26 [0.82 , 1.95]
Jendoubi 2017	13	20	15	20	3.3%	0.87 [0.58 , 1.30]
Pirim 2006	13	23	19	22	3.5%	0.65 [0.44 , 0.97]
Gilabert Morell 2002	25	44	15	22	3.6%	0.83 [0.57 , 1.22]
Remérand 2009	28	79	36	75	3.7%	0.74 [0.51 , 1.08]
Aubrun 2008	23	45	32	45	4.3%	0.72 [0.51 , 1.01]
Leal 2013	18	20	15	20	5.2%	1.20 [0.90 , 1.61]
Leal 2015	22	28	21	28	5.3%	1.05 [0.79 , 1.40]
Total (95% CI)		**3263**		**2702**	**100.0%**	**0.88 [0.81 , 0.96]**
Total events:	761		731			

Heterogeneity: Tau² = 0.01; Chi² = 99.14, df = 90 (P = 0.24); I² = 9%

Test for overall effect: Z = 2.87 (P = 0.004)

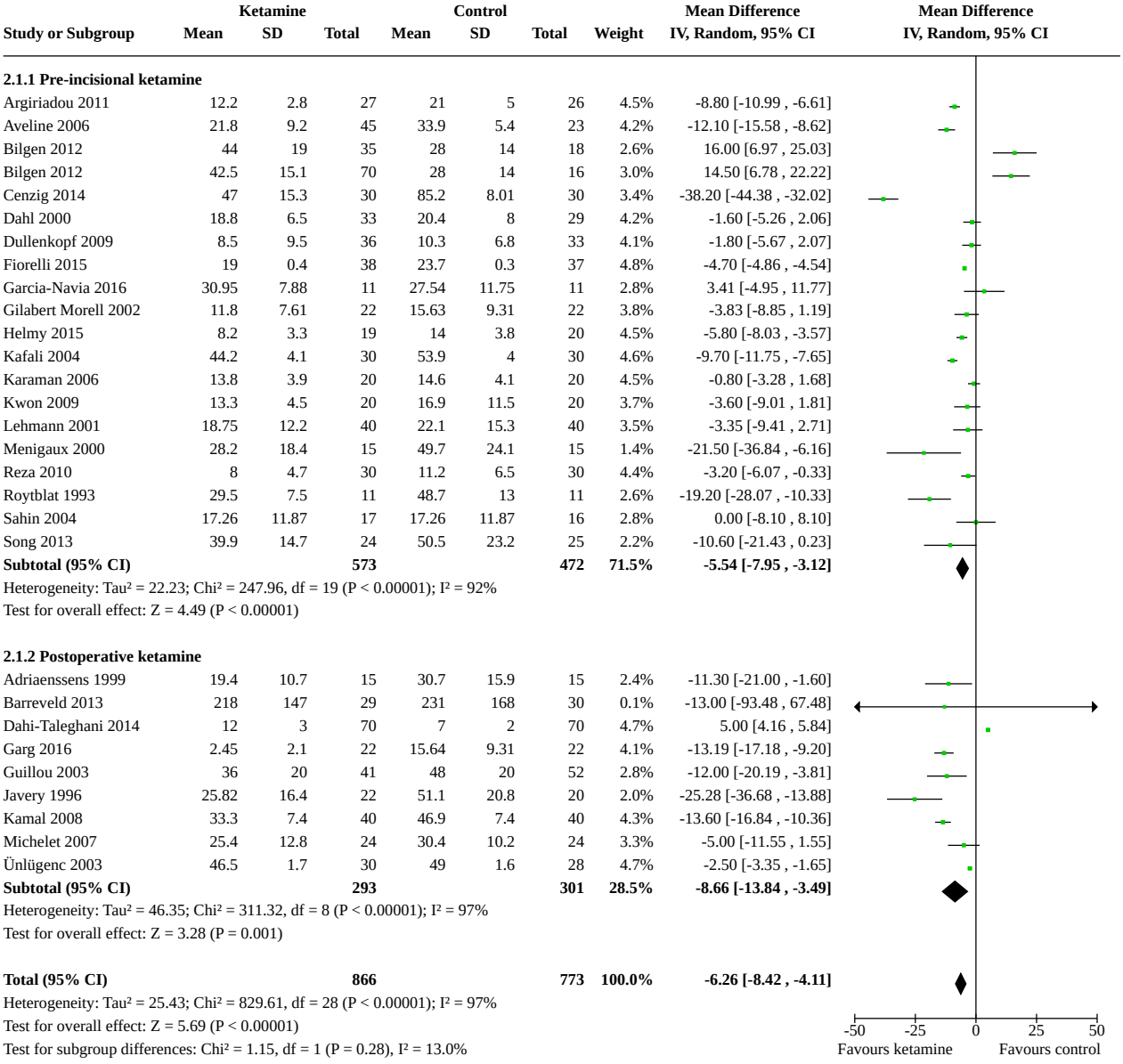
Test for subgroup differences: Not applicable



Comparison 2. Pre-incisional and postoperative ketamine versus control in a non-stratified patient population

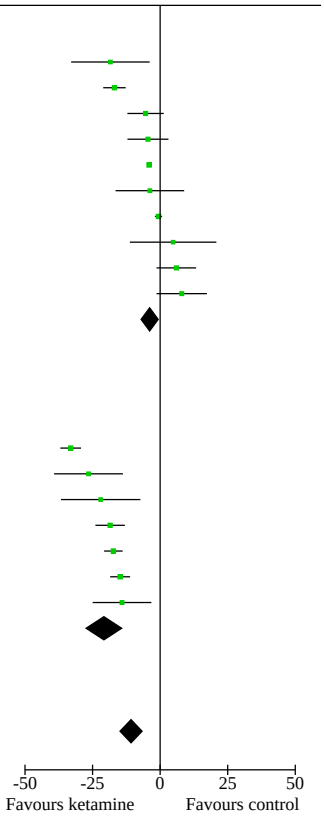
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Opioid consumption at 24 hours	28	1639	Mean Difference (IV, Random, 95% CI)	-6.26 [-8.42, -4.11]
2.1.1 Pre-incisional ketamine	19	1045	Mean Difference (IV, Random, 95% CI)	-5.54 [-7.95, -3.12]
2.1.2 Postoperative ketamine	9	594	Mean Difference (IV, Random, 95% CI)	-8.66 [-13.84, -3.49]
2.2 Opioid consumption at 48 hours	16	959	Mean Difference (IV, Random, 95% CI)	-10.76 [-14.84, -6.68]
2.2.1 Pre-incisional ketamine	9	534	Mean Difference (IV, Random, 95% CI)	-3.88 [-7.04, -0.72]
2.2.2 Postoperative ketamine	7	425	Mean Difference (IV, Random, 95% CI)	-20.81 [-27.39, -14.24]
2.3 Pain intensity at 24 hours	29	1646	Mean Difference (IV, Random, 95% CI)	-7.08 [-9.56, -4.59]
2.3.1 Pre-incisional ketamine	20	1075	Mean Difference (IV, Random, 95% CI)	-6.65 [-10.06, -3.24]
2.3.2 Postoperative ketamine	9	571	Mean Difference (IV, Random, 95% CI)	-8.30 [-12.55, -4.05]
2.4 Pain intensity at 48 hours	15	840	Mean Difference (IV, Random, 95% CI)	-5.49 [-7.72, -3.25]
2.4.1 Pre-incisional ketamine	9	509	Mean Difference (IV, Random, 95% CI)	-4.36 [-7.53, -1.19]
2.4.2 Postoperative ketamine	6	331	Mean Difference (IV, Random, 95% CI)	-8.02 [-15.79, -0.26]
2.5 Time to first request for analgesia/first trigger of PCA	13	643	Mean Difference (IV, Random, 95% CI)	37.70 [20.87, 54.52]

Analysis 2.1. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 1: Opioid consumption at 24 hours



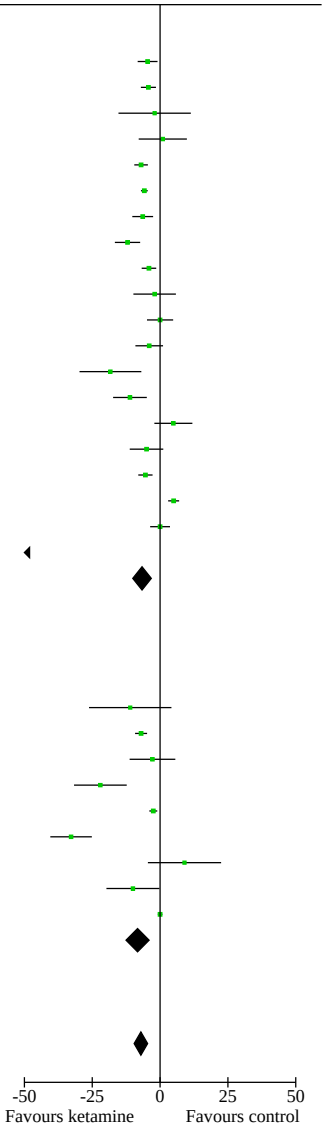
Analysis 2.2. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Pre-incisional ketamine								
Song 2013	77.3	20.2	24	95.7	30.8	25	3.9%	-18.40 [-32.93 , -3.87]
Kafali 2004	69.8	8	30	86.7	8.4	30	7.1%	-16.90 [-21.05 , -12.75]
Gilabert Morell 2002	17.21	9.85	22	22.6	12.72	22	6.4%	-5.39 [-12.11 , 1.33]
Kwon 2009	25.4	6.1	20	29.9	16.2	20	6.1%	-4.50 [-12.09 , 3.09]
Fiorelli 2015	20.7	0.3	38	24.8	0.3	37	7.7%	-4.10 [-4.24 , -3.96]
Dahl 2000	40.1	24.3	33	43.9	26.4	29	4.4%	-3.80 [-16.49 , 8.89]
Papaziogas 2001	0.28	1.15	18	0.88	2.56	17	7.6%	-0.60 [-1.93 , 0.73]
Menigaux 2000	34.3	23.2	15	29.5	21.5	15	3.5%	4.80 [-11.21 , 20.81]
Bilgen 2012	44	14.7	70	38	14	18	6.2%	6.00 [-1.33 , 13.33]
Bilgen 2012	46	19	35	38	14	16	5.5%	8.00 [-1.31 , 17.31]
Subtotal (95% CI)			**305**			**229**	**58.3%**	**-3.88 [-7.04 , -0.72]**
Heterogeneity: Tau² = 13.52; Chi² = 81.91, df = 9 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.41 (P = 0.02)								
2.2.2 Postoperative ketamine								
Arikan 2016	32.6	9.2	40	65.7	8.2	40	7.2%	-33.10 [-36.92 , -29.28]
Adriaenssens 1999	27.6	12.4	15	54.1	21.9	15	4.4%	-26.50 [-39.24 , -13.76]
Guillou 2003	58	35	41	80	37	52	3.8%	-22.00 [-36.69 , -7.31]
Garg 2016	2.59	2	22	21.09	12.88	22	6.8%	-18.50 [-23.95 , -13.05]
Kamal 2008	66.7	4.94	40	84	9.9	40	7.3%	-17.30 [-20.73 , -13.87]
Lak 2010	3	2	25	17.8	9.2	25	7.2%	-14.80 [-18.49 , -11.11]
Michelet 2007	41.7	17.9	24	55.8	20.4	24	5.0%	-14.10 [-24.96 , -3.24]
Subtotal (95% CI)			**207**			**218**	**41.7%**	**-20.81 [-27.39 , -14.24]**
Heterogeneity: Tau² = 62.08; Chi² = 56.94, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 6.21 (P < 0.00001)								
Total (95% CI)			**512**			**447**	**100.0%**	**-10.76 [-14.84 , -6.68]**
Heterogeneity: Tau² = 56.41; Chi² = 439.77, df = 16 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 5.17 (P < 0.00001)								
Test for subgroup differences: Chi² = 20.71, df = 1 (P < 0.00001), I² = 95.2%								



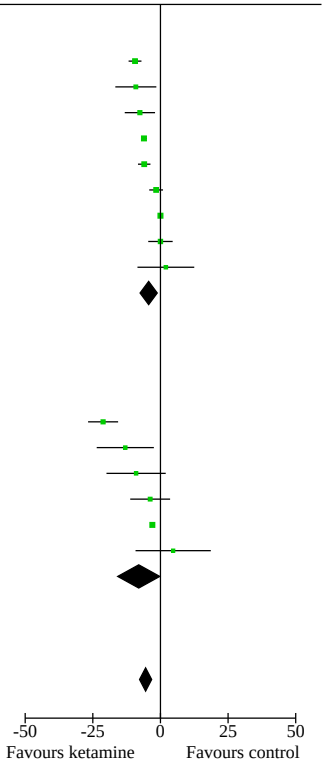
Analysis 2.3. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 3: Pain intensity at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Pre-incisional ketamine								
Aveline 2006	32.4	7.8	45	37	7	23	4.0%	-4.60 [-8.26 , -0.94]
Cenzig 2014	2	4.8	30	6.3	6.1	30	4.2%	-4.30 [-7.08 , -1.52]
D'Alonzo 2011	26	22	20	28	21	20	1.9%	-2.00 [-15.33 , 11.33]
Dahl 2000	59	22	60	58	19	29	2.8%	1.00 [-7.88 , 9.88]
Fiorelli 2015	41	5	38	48	6	37	4.2%	-7.00 [-9.50 , -4.50]
Kafali 2004	11.3	2.7	30	17.1	2.2	30	4.4%	-5.80 [-7.05 , -4.55]
Kwok 2004	9.2	10	45	15.6	8.5	45	4.0%	-6.40 [-10.23 , -2.57]
Kwon 2009	2	7	20	14	8	20	3.8%	-12.00 [-16.66 , -7.34]
Lebrun 2006	31.3	6.3	31	35.4	4.2	30	4.2%	-4.10 [-6.78 , -1.42]
Lee 2008	34	9	15	36	13	16	3.1%	-2.00 [-9.83 , 5.83]
Lehmann 2001	11	11	40	11	11	40	3.8%	0.00 [-4.82 , 4.82]
Mathisen 1999	10	6	16	14	9	18	3.7%	-4.00 [-9.09 , 1.09]
Menigaux 2000	24.3	10.7	15	42.6	19.8	15	2.3%	-18.30 [-29.69 , -6.91]
Menigaux 2001	15.2	12.2	25	26.3	10.1	25	3.5%	-11.10 [-17.31 , -4.89]
Nesek-Adam 2012	23.3	11.3	20	18.4	11.3	20	3.3%	4.90 [-2.10 , 11.90]
Papaziogas 2001	0.00001	0.00001	18	5	13	17	3.5%	-5.00 [-11.18 , 1.18]
Patel 2016	21	3	25	26.4	6	25	4.2%	-5.40 [-8.03 , -2.77]
Reza 2010	35	4	30	30	4	30	4.3%	5.00 [2.98 , 7.02]
Roytblat 1993	6	3.9	11	6	4.8	11	4.0%	0.00 [-3.65 , 3.65]
Safavi 2011	0.7	1.3	30	59	20	30	3.2%	-58.30 [-65.47 , -51.13]
Subtotal (95% CI)			**564**			**511**	**72.2%**	**-6.65 [-10.06 , -3.24]**
Heterogeneity: Tau² = 52.23; Chi² = 348.37, df = 19 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.82 (P = 0.0001)								
2.3.2 Postoperative ketamine								
Adriaenssens 1999	25	18	15	36	24	15	1.7%	-11.00 [-26.18 , 4.18]
Dahi-Taleghani 2014	10	5	70	17	8	70	4.3%	-7.00 [-9.21 , -4.79]
Guillou 2003	21.8	21.8	41	24.6	18.9	52	2.9%	-2.80 [-11.22 , 5.62]
Javery 1996	23	16.7	22	45	15.4	20	2.6%	-22.00 [-31.71 , -12.29]
Kamal 2008	26	2.5	40	28.5	4	40	4.3%	-2.50 [-3.96 , -1.04]
Lak 2010	32.8	14	25	65.6	13.6	25	3.1%	-32.80 [-40.45 , -25.15]
Lo 2008	41	20.2	15	32	17.4	15	1.9%	9.00 [-4.49 , 22.49]
Michelet 2007	30	14	24	40	20	24	2.6%	-10.00 [-19.77 , -0.23]
Ünlügenc 2003	10	1	30	10	2	28	4.4%	0.00 [-0.82 , 0.82]
Subtotal (95% CI)			**282**			**289**	**27.8%**	**-8.30 [-12.55 , -4.05]**
Heterogeneity: Tau² = 27.86; Chi² = 126.53, df = 8 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
Total (95% CI)			**846**			**800**	**100.0%**	**-7.08 [-9.56 , -4.59]**
Heterogeneity: Tau² = 36.44; Chi² = 507.34, df = 28 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 5.59 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%								



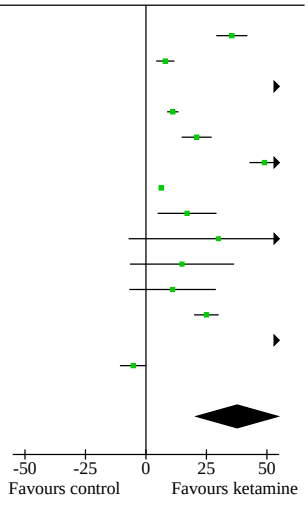
Analysis 2.4. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 4: Pain intensity at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Pre-incisional ketamine								
Lebrun 2006	26	4.2	31	35.4	5.2	30	9.4%	-9.40 [-11.78 , -7.02]
Menigaux 2000	15.2	7.6	15	24.3	12.9	15	4.8%	-9.10 [-16.68 , -1.52]
Menigaux 2001	8.1	10.1	25	15.7	10.1	25	6.3%	-7.60 [-13.20 , -2.00]
Kafali 2004	6	2.1	30	12.1	2.1	30	10.2%	-6.10 [-7.16 , -5.04]
Fiorelli 2015	27	6	38	33	4	37	9.4%	-6.00 [-8.30 , -3.70]
Aveline 2006	33.4	5.2	45	35	5	23	9.2%	-1.60 [-4.15 , 0.95]
Papaziogas 2001	1e-7	1e-7	18	0.000001	0.00001	18	10.5%	-0.00 [-0.00 , 0.00]
Kwon 2009	2	5	20	2	9	20	7.3%	0.00 [-4.51 , 4.51]
Dahl 2000	47	23	60	45	24	29	3.2%	2.00 [-8.50 , 12.50]
Subtotal (95% CI)			**282**			**227**	**70.2%**	**-4.36 [-7.53 , -1.19]**
Heterogeneity: Tau² = 18.84; Chi² = 227.02, df = 8 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.69 (P = 0.007)								
2.4.2 Postoperative ketamine								
Lak 2010	24.8	10.4	25	46	9.6	25	6.4%	-21.20 [-26.75 , -15.65]
Michelet 2007	29	16	24	42	21	24	3.1%	-13.00 [-23.56 , -2.44]
Adriaenssens 1999	12	12	15	21	18	15	3.0%	-9.00 [-19.95 , 1.95]
Guillou 2003	15.1	18	41	18.9	18	52	4.9%	-3.80 [-11.17 , 3.57]
Kamal 2008	19	1	40	22	2	40	10.4%	-3.00 [-3.69 , -2.31]
Lo 2008	16.7	22.9	15	12	15.2	15	2.1%	4.70 [-9.21 , 18.61]
Subtotal (95% CI)			**160**			**171**	**29.8%**	**-8.02 [-15.79 , -0.26]**
Heterogeneity: Tau² = 74.85; Chi² = 46.27, df = 5 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.03 (P = 0.04)								
Total (95% CI)			**442**			**398**	**100.0%**	**-5.49 [-7.72 , -3.25]**
Heterogeneity: Tau² = 12.45; Chi² = 364.99, df = 14 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%								



Analysis 2.5. Comparison 2: Pre-incisional and postoperative ketamine versus control in a non-stratified patient population, Outcome 5: Time to first request for analgesia/first trigger of PCA

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aqil 2011	52.5	22.7	60	17	5.67	15	7.4%	35.50 [29.08 , 41.92]
Aqil 2011	25	6.85	30	17	5.67	15	7.4%	8.00 [4.23 , 11.77]
Ataskhoyi 2013	165	28	30	17	8.5	30	7.2%	148.00 [137.53 , 158.47]
Cenzig 2014	22.73	5.72	30	11.63	3.21	30	7.4%	11.10 [8.75 , 13.45]
Gilabert Morell 2002	26.45	11.65	22	5.47	9.19	22	7.4%	20.98 [14.78 , 27.18]
Helmy 2015	82	12	19	33	7	20	7.4%	49.00 [42.79 , 55.21]
Kafali 2004	17.7	2.2	30	11.4	1.2	30	7.5%	6.30 [5.40 , 7.20]
Menigaux 2000	27	23	15	10	7	15	7.2%	17.00 [4.83 , 29.17]
Nesek-Adam 2012	108	60	20	78	60	20	5.5%	30.00 [-7.19 , 67.19]
Ong 2001	42.8	46.9	20	27.9	14.6	20	6.6%	14.90 [-6.63 , 36.43]
Papaziogas 2001	132	34	18	121	18	17	6.9%	11.00 [-6.89 , 28.89]
Roytblat 1993	35	5	11	10	7	11	7.4%	25.00 [19.92 , 30.08]
Safavi 2011	170	17.3	30	17.5	5.7	30	7.4%	152.50 [145.98 , 159.02]
Sahin 2004	5.47	3.32	17	10.69	10.83	16	7.4%	-5.22 [-10.76 , 0.32]
Total (95% CI)			**352**			**291**	**100.0%**	**37.70 [20.87 , 54.52]**
Heterogeneity: Tau² = 988.82; Chi² = 2849.56, df = 13 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 4.39 (P < 0.0001)								
Test for subgroup differences: Not applicable								



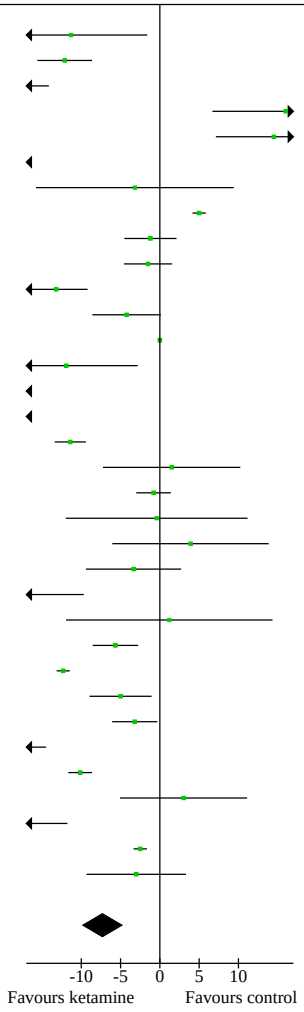
Comparison 3. Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Opioid consumption at 24 hours	33	2176	Mean Difference (IV, Random, 95% CI)	-7.31 [-9.78, -4.84]
3.2 Opioid consumption at 48 hours	15	1110	Mean Difference (IV, Random, 95% CI)	-14.78 [-21.12, -8.44]
3.3 Pain intensity at rest at 24 hours	32	2053	Mean Difference (IV, Random, 95% CI)	-8.13 [-10.84, -5.42]
3.4 Pain intensity during movement at 24 hours	10	613	Mean Difference (IV, Random, 95% CI)	-6.50 [-18.97, 5.97]
3.5 Pain intensity at rest at 48 hours	18	1202	Mean Difference (IV, Random, 95% CI)	-6.38 [-9.91, -2.84]
3.6 Pain intensity during movement at 48 hours	8	523	Mean Difference (IV, Random, 95% CI)	-4.47 [-13.08, 4.14]

Analysis 3.1. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	19.4	10.7	15	30.7	15.9	15	2.3%	-11.30 [-21.00 , -1.60]
Aveline 2006	21.8	9.2	45	33.9	5.4	23	3.3%	-12.10 [-15.58 , -8.62]
Aveline 2009	39.2	6.5	25	56.8	5.9	24	3.3%	-17.60 [-21.07 , -14.13]
Bilgen 2012	44	19	35	28	14	16	2.4%	16.00 [6.69 , 25.31]
Bilgen 2012	42.5	15.1	70	28	14	18	2.7%	14.50 [7.13 , 21.87]
Cenzig 2014	47	15.3	30	85.2	8.01	30	2.9%	-38.20 [-44.38 , -32.02]
Crousier 2008	13	6.6	12	16.17	26	18	1.9%	-3.17 [-15.75 , 9.41]
Dahi-Taleghani 2014	12	3	70	7	2	70	3.5%	5.00 [4.16 , 5.84]
Dahl 2000	19.2	6.3	60	20.4	8	29	3.3%	-1.20 [-4.52 , 2.12]
Dullenkopf 2009	8.8	9	77	10.3	6.8	33	3.4%	-1.50 [-4.57 , 1.57]
Garg 2016	2.45	2.1	22	15.64	9.31	22	3.3%	-13.19 [-17.18 , -9.20]
Gilabert Morell 2002	11.4	6.7	44	15.63	9.31	22	3.2%	-4.23 [-8.60 , 0.14]
Grady 2012	1e-7	1e-8	30	0.000001	0.000001	32	3.6%	-0.00 [-0.00 , -0.00]
Guillou 2003	35.9	22.2	41	47.8	22.2	52	2.4%	-11.90 [-20.99 , -2.81]
Hadi 2010	35.2	8.9	30	60	2.6	15	3.3%	-24.80 [-28.25 , -21.35]
Hadi 2013	35.2	8.9	30	60	2.6	15	3.3%	-24.80 [-28.25 , -21.35]
Haliloglu 2015	25	3.7	26	36.4	3.6	26	3.5%	-11.40 [-13.38 , -9.42]
Hercock 1999	34.5	15.2	24	33	16	25	2.5%	1.50 [-7.24 , 10.24]
Karaman 2006	13.8	4.1	40	14.6	4.1	20	3.5%	-0.80 [-3.00 , 1.40]
Katz 2004	51.9	33.3	97	52.3	32.8	46	2.0%	-0.40 [-11.97 , 11.17]
Leal 2013	29	18.4	20	25.1	13.3	20	2.3%	3.90 [-6.05 , 13.85]
Lehmann 2001	18.75	12.2	40	22.1	15.3	40	2.9%	-3.35 [-9.41 , 2.71]
Menigaux 2000	26.2	17.9	30	49.7	24.2	15	1.7%	-23.50 [-37.32 , -9.68]
Murdoch 2002	67.6	25.1	21	66.4	17.7	21	1.8%	1.20 [-11.94 , 14.34]
Ögün 2001	10.62	4.6	16	16.27	3.58	15	3.4%	-5.65 [-8.54 , -2.76]
Parikh 2011	5.8	1.48	30	18.1	1.8	30	3.5%	-12.30 [-13.13 , -11.47]
Remérand 2009	14	13	79	19	12	75	3.3%	-5.00 [-8.95 , -1.05]
Reza 2010	8	4.7	30	11.2	6.5	30	3.4%	-3.20 [-6.07 , -0.33]
Roytblat 1993	29.5	4.8	11	48.7	6.4	11	3.1%	-19.20 [-23.93 , -14.47]
Safavi 2011	1.864	0.43	30	12	4.2	30	3.5%	-10.14 [-11.65 , -8.63]
Sahin 2004	20.28	11.81	17	17.26	11.87	16	2.6%	3.02 [-5.06 , 11.10]
Sen 2009	28	8	20	48	17	20	2.6%	-20.00 [-28.23 , -11.77]
Ünlügenc 2003	46.5	1.7	30	49	1.6	28	3.5%	-2.50 [-3.35 , -1.65]
Zakine 2008	22.3	15.1	50	25.3	12.6	27	2.9%	-3.00 [-9.33 , 3.33]
Total (95% CI)			**1247**			**929**	**100.0%**	**-7.31 [-9.78 , -4.84]**

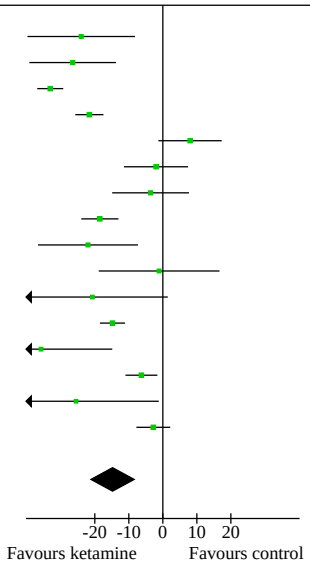
Heterogeneity: Tau² = 44.67; Chi² = 2205.12, df = 33 (P < 0.00001); I² = 99%
Test for overall effect: Z = 5.80 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	45	20	20	69	30	20	5.3%	-24.00 [-39.80 , -8.20]
Adriaenssens 1999	27.6	12.4	15	54.1	21.9	15	6.0%	-26.50 [-39.24 , -13.76]
Arikan 2016	32.6	9.2	40	65.7	8.2	40	7.8%	-33.10 [-36.92 , -29.28]
Aveline 2009	50.5	5.7	25	72.1	8.7	24	7.7%	-21.60 [-25.74 , -17.46]
Bilgen 2012	46	19	35	38	14	16	6.8%	8.00 [-1.31 , 17.31]
Bilgen 2012	44	14.7	70	46	19	18	6.8%	-2.00 [-11.43 , 7.43]
Dahl 2000	40.3	23.4	60	43.9	26.4	29	6.4%	-3.60 [-14.89 , 7.69]
Garg 2016	2.59	2	22	21.1	12.9	22	7.5%	-18.51 [-23.96 , -13.06]
Guillou 2003	58	35	41	80	37	52	5.6%	-22.00 [-36.69 , -7.31]
Katz 2004	81	51.6	97	82.1	50.1	46	4.9%	-1.10 [-18.85 , 16.65]
Kim 2013	61.9	36.6	35	82.6	39	17	4.0%	-20.70 [-42.85 , 1.45]
Lak 2010	3	2	25	17.8	9.2	25	7.8%	-14.80 [-18.49 , -11.11]
Menigaux 2000	31.9	22.1	30	67.7	38.3	15	4.3%	-35.80 [-56.73 , -14.87]
Remérand 2009	20.7	14.4	79	27	15.3	75	7.7%	-6.30 [-11.00 , -1.60]
Snijdelaar 2004	47.9	26.2	13	73.4	34.8	12	3.7%	-25.50 [-49.80 , -1.20]
Zakine 2008	9.5	10.5	50	12.3	10.7	27	7.6%	-2.80 [-7.78 , 2.18]
Total (95% CI)			**657**			**453**	**100.0%**	**-14.78 [-21.12 , -8.44]**

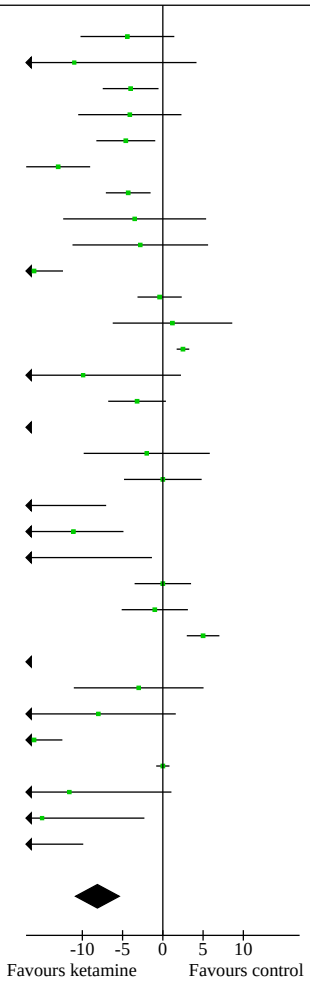
Heterogeneity: Tau² = 131.04; Chi² = 178.25, df = 15 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.57 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	28.1	9.4	20	32.5	9.4	20	3.3%	-4.40 [-10.23 , 1.43]
Adriaenssens 1999	25	18	15	36	24	15	1.8%	-11.00 [-26.18 , 4.18]
Arikan 2016	27	5	40	31	10	40	3.7%	-4.00 [-7.46 , -0.54]
Aubrun 2008	15.2	11.8	45	19.3	18.5	45	3.2%	-4.10 [-10.51 , 2.31]
Aveline 2006	32.4	7.8	45	37	7	23	3.7%	-4.60 [-8.26 , -0.94]
Aveline 2009	24	6	25	37	8	24	3.6%	-13.00 [-16.97 , -9.03]
Cenzig 2014	2	4.8	30	6.3	6.1	30	3.8%	-4.30 [-7.08 , -1.52]
Dahl 2000	54.5	22	60	58	19	29	2.8%	-3.50 [-12.38 , 5.38]
Guillou 2003	21.8	21.8	41	24.6	18.9	52	2.8%	-2.80 [-11.22 , 5.62]
Hadi 2013	40	7	30	56	5.1	15	3.7%	-16.00 [-19.60 , -12.40]
Haliloglu 2015	4.2	5	26	4.6	5.1	26	3.8%	-0.40 [-3.15 , 2.35]
Hercock 1999	14	12.5	24	12.8	14	25	3.0%	1.20 [-6.22 , 8.62]
Katz 2004	19.4	2.8	97	16.9	1.9	46	3.9%	2.50 [1.72 , 3.28]
Kim 2013	36.1	16	35	46	23	17	2.2%	-9.90 [-22.05 , 2.25]
Kwok 2004	12.4	12.5	90	15.6	8.5	45	3.7%	-3.20 [-6.78 , 0.38]
Lak 2010	32.8	14	25	65.6	13.6	25	3.0%	-32.80 [-40.45 , -25.15]
Lee 2008	34	9	15	36	13	16	3.0%	-2.00 [-9.83 , 5.83]
Lehmann 2001	11	11	40	11	11	40	3.5%	0.00 [-4.82 , 4.82]
Menigaux 2000	24.7	11.7	30	42.6	19.8	15	2.4%	-17.90 [-28.76 , -7.04]
Menigaux 2001	15.2	12.2	25	26.3	10.1	25	3.3%	-11.10 [-17.31 , -4.89]
Ögün 2001	17	20	16	36	29	15	1.5%	-19.00 [-36.65 , -1.35]
Parikh 2011	21.4	2.4	30	21.4	9.5	30	3.7%	0.00 [-3.51 , 3.51]
Remérand 2009	14	14	79	15	12	75	3.6%	-1.00 [-5.11 , 3.11]
Reza 2010	35	4	30	30	4	30	3.8%	5.00 [2.98 , 7.02]
Safavi 2011	0.7	1.3	30	59	20	30	3.1%	-58.30 [-65.47 , -51.13]
Sen 2009	10	13	20	13	13	20	2.9%	-3.00 [-11.06 , 5.06]
Snijdelaar 2004	12	10	13	20	14	12	2.6%	-8.00 [-17.61 , 1.61]
Suzuki 2006	9	4	24	25	8	25	3.7%	-16.00 [-19.52 , -12.48]
Ünlügenc 2003	10	1	30	10	2	28	3.9%	0.00 [-0.82 , 0.82]
Yamauchi 2008	10.1	15.3	45	21.7	29	23	2.1%	-11.60 [-24.27 , 1.07]
Yeom 2012	36	20	20	51	21	20	2.1%	-15.00 [-27.71 , -2.29]
Zakine 2008	16.7	15.9	50	35	19	27	2.9%	-18.30 [-26.71 , -9.89]
Total (95% CI)			**1145**			**908**	**100.0%**	**-8.13 [-10.84 , -5.42]**

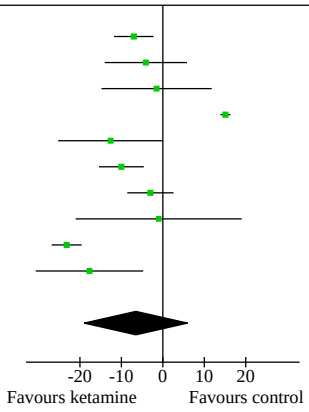
Heterogeneity: Tau² = 48.67; Chi² = 667.39, df = 31 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.88 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 4: Pain intensity during movement at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aveline 2009	48	9	25	55	8	24	10.5%	-7.00 [-11.76 , -2.24]
Guillou 2003	37.1	26.8	41	41.2	20.6	52	10.0%	-4.10 [-14.03 , 5.83]
Hercock 1999	41.7	23.2	24	43.2	24.3	25	9.5%	-1.50 [-14.80 , 11.80]
Katz 2004	55.7	2.4	97	40.6	3.8	46	10.7%	15.10 [13.90 , 16.30]
Kim 2013	45.4	19.2	35	58	23	17	9.6%	-12.60 [-25.25 , 0.05]
Menigaux 2000	48	10	30	58	8	15	10.5%	-10.00 [-15.40 , -4.60]
Sen 2009	15	9	20	18	9	20	10.5%	-3.00 [-8.58 , 2.58]
Snijdelaar 2004	27	25	13	28	26	12	8.4%	-1.00 [-21.03 , 19.03]
Suzuki 2006	25.7	6	24	48.9	6.9	25	10.6%	-23.20 [-26.82 , -19.58]
Yamauchi 2008	31.1	23.3	45	48.8	27	23	9.6%	-17.70 [-30.67 , -4.73]
Total (95% CI)			**354**			**259**	**100.0%**	**-6.50 [-18.97 , 5.97]**

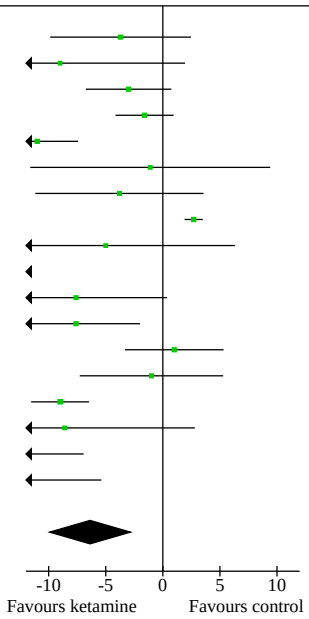
Heterogeneity: Tau² = 378.24; Chi² = 549.49, df = 9 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 5: Pain intensity at rest at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	16.3	11.9	20	20	7.5	20	5.8%	-3.70 [-9.86 , 2.46]
Adriaenssens 1999	12	12	15	21	18	15	4.2%	-9.00 [-19.95 , 1.95]
Arikan 2016	25	11	40	28	5	40	6.5%	-3.00 [-6.74 , 0.74]
Aveline 2006	33.4	5.2	45	35	5	23	6.8%	-1.60 [-4.15 , 0.95]
Aveline 2009	24	4	25	35	8	24	6.5%	-11.00 [-14.56 , -7.44]
Dahl 2000	43.9	23.1	60	45	24	29	4.3%	-1.10 [-11.61 , 9.41]
Guillou 2003	15.1	18	41	18.9	18	52	5.4%	-3.80 [-11.17 , 3.57]
Katz 2004	14	2.9	97	11.3	1.9	46	7.0%	2.70 [1.90 , 3.50]
Kim 2013	29	18.6	35	34	20	17	4.1%	-5.00 [-16.33 , 6.33]
Lak 2010	24.8	10.4	25	46	9.6	25	6.0%	-21.20 [-26.75 , -15.65]
Menigaux 2000	16.7	12.8	30	24.3	12.9	15	5.2%	-7.60 [-15.57 , 0.37]
Menigaux 2001	8.1	10.1	25	15.7	10.1	25	6.0%	-7.60 [-13.20 , -2.00]
Remérand 2009	15	16	79	14	11	75	6.3%	1.00 [-3.32 , 5.32]
Snijdelaar 2004	8	8	13	9	8	12	5.7%	-1.00 [-7.28 , 5.28]
Suzuki 2006	9	4	24	18	5	25	6.8%	-9.00 [-11.53 , -6.47]
Yamauchi 2008	7.1	19.9	45	15.7	24	23	4.1%	-8.60 [-20.00 , 2.80]
Yeom 2012	24	14	20	42	21	20	4.2%	-18.00 [-29.06 , -6.94]
Zakine 2008	12.2	13.5	50	25	17	27	5.4%	-12.80 [-20.22 , -5.38]
Total (95% CI)			**689**			**513**	**100.0%**	**-6.38 [-9.91 , -2.84]**

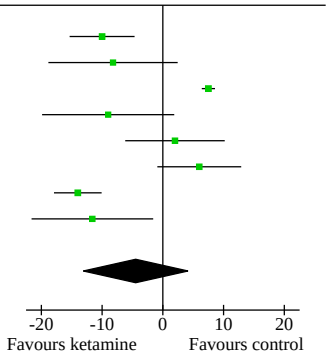
Heterogeneity: Tau² = 46.53; Chi² = 229.74, df = 17 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Perioperative ketamine versus control co-administered with nitrous oxide in a non-stratified study population, Outcome 6: Pain intensity during movement at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aveline 2009	49	6	25	59	12	24	13.2%	-10.00 [-15.35 , -4.65]
Guillou 2003	26.8	26.8	41	35	24.7	51	11.4%	-8.20 [-18.84 , 2.44]
Katz 2004	46.5	3.3	97	39	3	46	13.8%	7.50 [6.41 , 8.59]
Kim 2013	36	18.3	35	45	19	17	11.4%	-9.00 [-19.88 , 1.88]
Menigaux 2000	38	18	30	36	10	15	12.3%	2.00 [-6.19 , 10.19]
Snijdelaar 2004	11	12	13	5	4	12	12.7%	6.00 [-0.90 , 12.90]
Suzuki 2006	29	7	24	43	7	25	13.5%	-14.00 [-17.92 , -10.08]
Yamauchi 2008	26.2	19.8	45	37.8	20	23	11.7%	-11.60 [-21.61 , -1.59]
Total (95% CI)			**310**			**213**	**100.0%**	**-4.47 [-13.08 , 4.14]**

Heterogeneity: Tau² = 139.33; Chi² = 164.16, df = 7 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable

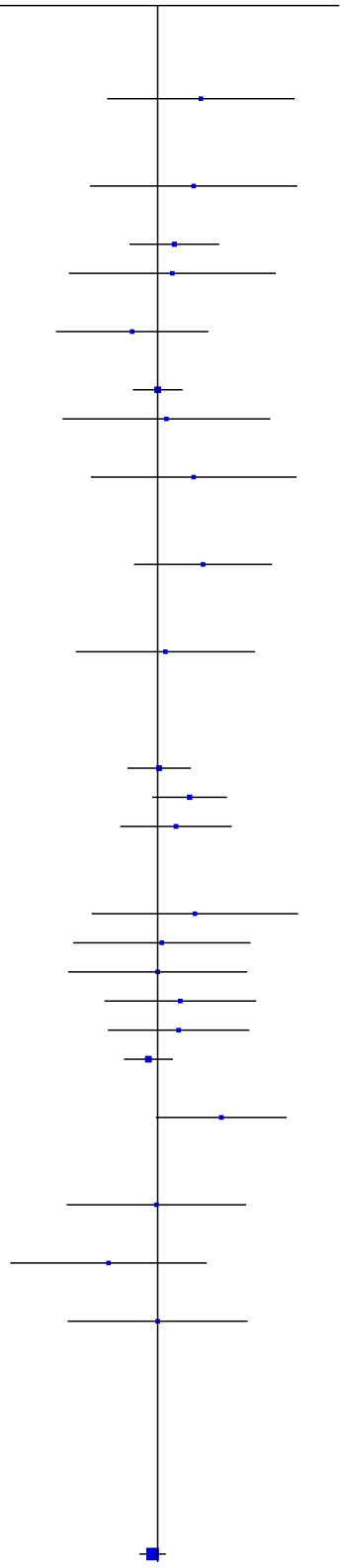


Comparison 4. CNS adverse events in studies with benzodiazepine premedication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 CNS adverse events	65	3943	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.38]

Analysis 4.1. Comparison 4: CNS adverse events in studies with benzodiazepine premedication, Outcome 1: CNS adverse events

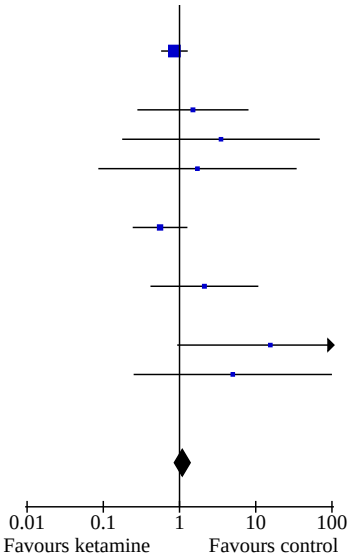
Study or Subgroup	Ketamine Events	Ketamine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Adam 2005	0	20	0	20		Not estimable
Adriaenssens 1999	0	15	0	15		Not estimable
Aqil 2011	5	90	0	30	0.7%	3.75 [0.21 , 65.84]
Argiriadou 2004	0	30	0	15		Not estimable
Argiriadou 2011	0	27	0	26		Not estimable
Arikan 2016	1	40	0	40	0.6%	3.00 [0.13 , 71.51]
Ataskhoyi 2013	0	30	0	30		Not estimable
Aubrun 2008	5	45	3	45	3.0%	1.67 [0.42 , 6.56]
Aveline 2006	1	45	0	23	0.6%	1.57 [0.07 , 36.98]
Aveline 2009	0	25	0	24		Not estimable
Chazan 2010	1	24	2	22	1.0%	0.46 [0.04 , 4.71]
De Kock 2001	0	40	0	20		Not estimable
Dualé 2009	8	20	8	20	9.9%	1.00 [0.47 , 2.14]
Dullenkopf 2009	1	77	0	33	0.6%	1.31 [0.05 , 31.29]
Fiorelli 2015	0	38	0	37		Not estimable
Galinski 2007	1	20	0	20	0.6%	3.00 [0.13 , 69.52]
Ganne 2005	0	30	0	31		Not estimable
Garcia-Navia 2016	0	11	0	11		Not estimable
Garg 2016	4	22	1	22	1.3%	4.00 [0.48 , 33.00]
Gilabert Morell 2002	0	44	0	22		Not estimable
Guignard 2002	0	25	0	25		Not estimable
Guillou 2003	1	41	1	52	0.8%	1.27 [0.08 , 19.67]
Hadi 2010	0	15	0	15		Not estimable
Hadi 2013	0	30	0	15		Not estimable
Hasanein 2011	0	30	0	30		Not estimable
Hayes 2004	6	22	6	23	6.1%	1.05 [0.40 , 2.75]
Hu 2014	7	31	4	47	4.4%	2.65 [0.85 , 8.31]
Ilkjaer 1998	3	24	2	28	2.0%	1.75 [0.32 , 9.62]
Jaksch 2002	0	15	0	15		Not estimable
Jendoubi 2017	0	20	0	20		Not estimable
Joly 2005	1	24	0	25	0.6%	3.12 [0.13 , 73.04]
Joseph 2012	1	22	1	25	0.8%	1.14 [0.08 , 17.11]
Kamal 2008	1	40	1	40	0.8%	1.00 [0.06 , 15.44]
Kararmaz 2003	2	20	1	20	1.1%	2.00 [0.20 , 20.33]
Katz 2004	4	97	1	46	1.2%	1.90 [0.22 , 16.50]
Kim 2016	8	28	11	29	10.2%	0.75 [0.36 , 1.59]
Kwon 2009	0	20	0	20		Not estimable
Leal 2013	7	20	1	20	1.4%	7.00 [0.95 , 51.80]
Lebrun 2006	0	54	0	30		Not estimable
Lehmann 2001	0	40	0	40		Not estimable
Loftus 2010	1	52	1	50	0.8%	0.96 [0.06 , 14.96]
Mahran 2015	0	30	0	30		Not estimable
Martinez 2014	0	34	2	38	0.6%	0.22 [0.01 , 4.48]
Mathisen 1999	0	32	0	18		Not estimable
Mebazaa MS 2008	1	67	1	67	0.8%	1.00 [0.06 , 15.66]
Mendola 2012	0	32	0	30		Not estimable
Menigaux 2000	0	30	0	15		Not estimable
Menigaux 2001	0	25	0	25		Not estimable
Michelet 2007	0	24	0	24		Not estimable
Pacreu 2012	0	10	0	10		Not estimable
Papaziogas 2001	0	18	0	17		Not estimable
Pirim 2006	0	23	0	22		Not estimable
Remérand 2009	28	79	31	75	35.3%	0.86 [0.57 , 1.28]



Analysis 4.1. (Continued)

Pirim 2006	0	23	0	22		Not estimable
Remérand 2009	28	79	31	75	35.3%	0.86 [0.57 , 1.28]
Roytblat 1993	0	11	0	11		Not estimable
Sen 2009	3	20	2	20	2.0%	1.50 [0.28 , 8.04]
Siddiqui 2015	2	29	0	20	0.6%	3.50 [0.18 , 69.23]
Singh 2013	2	60	0	20	0.6%	1.72 [0.09 , 34.42]
Snijdelaar 2004	0	13	0	12		Not estimable
Subramaniam 2011	5	15	9	15	8.3%	0.56 [0.24 , 1.27]
Suzuki 1999	0	105	0	35		Not estimable
Tena 2014	4	33	2	35	2.1%	2.12 [0.42 , 10.82]
Van Elstraete 2004	0	20	0	20		Not estimable
Yalcin 2012	7	26	0	27	0.7%	15.56 [0.93 , 259.28]
Yazigi 2012	2	30	0	30	0.6%	5.00 [0.25 , 99.95]
Zakine 2008	0	50	0	27		Not estimable
Total (95% CI)		**2179**		**1764**	**100.0%**	**1.09 [0.86 , 1.38]**
Total events:	123		91			

Heterogeneity: Tau² = 0.00; Chi² = 24.37, df = 30 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



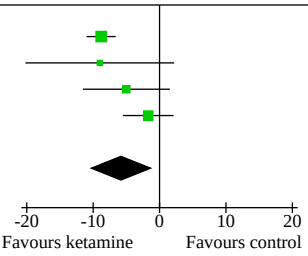
Comparison 5. Perioperative ketamine versus control: thoracotomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Opioid consumption at 24 hours	4	241	Mean Difference (IV, Random, 95% CI)	-5.81 [-10.28, -1.35]
5.2 Opioid consumption at 48 hours	3	191	Mean Difference (IV, Random, 95% CI)	-12.52 [-18.34, -6.71]
5.3 Pain intensity at rest at 24 hours	13	782	Mean Difference (IV, Random, 95% CI)	-3.90 [-8.80, 1.00]
5.4 Pain intensity during movement at 24 hours	5	315	Mean Difference (IV, Random, 95% CI)	-7.32 [-20.10, 5.45]
5.5 Pain intensity at rest at 48 hours	9	530	Mean Difference (IV, Random, 95% CI)	-6.86 [-10.37, -3.35]
5.6 Pain intensity during movement at 48 hours	5	298	Mean Difference (IV, Random, 95% CI)	-10.64 [-15.27, -6.00]

Analysis 5.1. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	12.2	2.8	27	21	5	26	36.3%	-8.80 [-10.99 , -6.61]
Dualé 2009	39	23	39	48	28	41	11.3%	-9.00 [-20.21 , 2.21]
Michelet 2007	25.4	12.8	24	30.4	10.2	24	21.4%	-5.00 [-11.55 , 1.55]
Ysasi 2010	23.1	7.3	30	24.8	7.7	30	30.9%	-1.70 [-5.50 , 2.10]
Total (95% CI)			**120**			**121**	**100.0%**	**-5.81 [-10.28 , -1.35]**

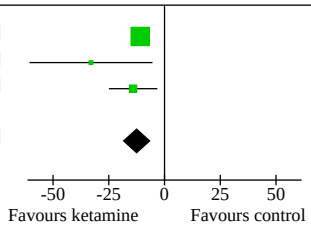
Heterogeneity: Tau² = 13.02; Chi² = 10.55, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	14.1	3.7	27	25	5.5	26	74.2%	-10.90 [-13.43 , -8.37]
Lahtinen 2004	154.5	66	44	187.5	67.5	46	4.2%	-33.00 [-60.58 , -5.42]
Michelet 2007	41.7	17.9	24	55.8	20.4	24	21.5%	-14.10 [-24.96 , -3.24]
Total (95% CI)			**95**			**96**	**100.0%**	**-12.52 [-18.34 , -6.71]**

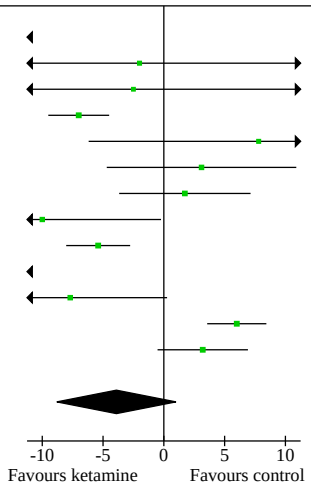
Heterogeneity: Tau² = 10.19; Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 4.22 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	22.3	3.4	27	39	10.2	26	8.8%	-16.70 [-20.83 , -12.57]
D'Alonzo 2011	26	22	20	28	21	20	5.6%	-2.00 [-15.33 , 11.33]
Dualé 2009	30	27.7	39	32.5	50	41	4.3%	-2.50 [-20.10 , 15.10]
Fiorelli 2015	41	5	38	48	6	37	9.2%	-7.00 [-9.50 , -4.50]
Joseph 2012	25	29	22	17.2	17.8	25	5.3%	7.80 [-6.18 , 21.78]
Lahtinen 2004	28.5	17.7	44	25.4	20	46	7.6%	3.10 [-4.69 , 10.89]
Mendola 2012	9.72	12.2	32	7.99	9.4	30	8.5%	1.73 [-3.67 , 7.13]
Michelet 2007	30	14	24	40	20	24	6.9%	-10.00 [-19.77 , -0.23]
Patel 2016	21	3	25	26.4	6	25	9.2%	-5.40 [-8.03 , -2.77]
Suzuki 2006	9	4	24	25	8	25	9.0%	-16.00 [-19.52 , -12.48]
Tena 2014	19.4	16.8	33	27.1	16.7	35	7.5%	-7.70 [-15.67 , 0.27]
Yazigi 2012	10	3.2	30	4	6	30	9.2%	6.00 [3.57 , 8.43]
Ysasi 2010	12.9	8.1	30	9.7	6.5	30	8.9%	3.20 [-0.52 , 6.92]
Total (95% CI)			**388**			**394**	**100.0%**	**-3.90 [-8.80 , 1.00]**

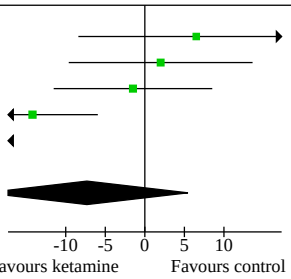
Heterogeneity: Tau² = 66.35; Chi² = 179.55, df = 12 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 4: Pain intensity during movement at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Joseph 2012	44.8	27.5	20	38.3	21.9	24	17.5%	6.50 [-8.40 , 21.40]
Yazigi 2012	26	25.5	30	24	20.1	30	19.3%	2.00 [-9.62 , 13.62]
Lahtinen 2004	47.7	23.1	44	49.2	25.4	46	20.1%	-1.50 [-11.52 , 8.52]
Tena 2014	21.5	17.7	33	35.7	17	35	20.9%	-14.20 [-22.46 , -5.94]
Argiriadou 2011	26.5	7.4	27	51.5	8.8	26	22.3%	-25.00 [-29.39 , -20.61]
Total (95% CI)			**154**			**161**	**100.0%**	**-7.32 [-20.10 , 5.45]**

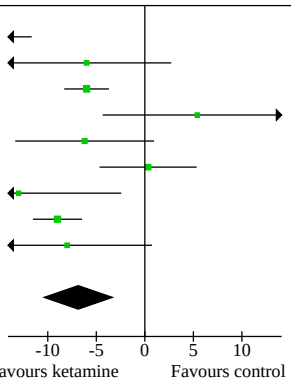
Heterogeneity: Tau² = 185.61; Chi² = 42.21, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 5: Pain intensity at rest at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	13.6	6.8	27	30.5	11.9	26	12.7%	-16.90 [-22.14 , -11.66]
Chazan 2010	18	11	24	24	18	22	8.5%	-6.00 [-14.71 , 2.71]
Fiorelli 2015	27	6	38	33	4	37	16.5%	-6.00 [-8.30 , -3.70]
Joseph 2012	18.6	16.3	22	13.2	17.8	25	7.5%	5.40 [-4.35 , 15.15]
Lahtinen 2004	12.3	16.9	44	18.5	17.7	46	10.2%	-6.20 [-13.35 , 0.95]
Mendola 2012	6.42	11.3	32	6.08	8.7	30	13.1%	0.34 [-4.66 , 5.34]
Michelet 2007	29	16	24	42	21	24	6.8%	-13.00 [-23.56 , -2.44]
Suzuki 2006	9	4	24	18	5	25	16.3%	-9.00 [-11.53 , -6.47]
Yazigi 2012	9	14	30	17	20	30	8.5%	-8.00 [-16.74 , 0.74]
Total (95% CI)			**265**			**265**	**100.0%**	**-6.86 [-10.37 , -3.35]**

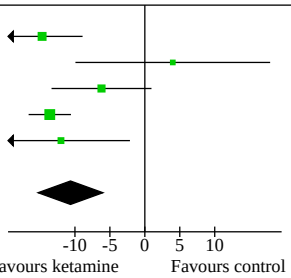
Heterogeneity: Tau² = 18.03; Chi² = 32.61, df = 8 (P < 0.0001); I² = 75%
Test for overall effect: Z = 3.83 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Perioperative ketamine versus control: thoracotomy, Outcome 6: Pain intensity during movement at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Argiriadou 2011	20.6	7.4	27	35.3	13.2	26	24.1%	-14.70 [-20.49 , -8.91]
Joseph 2012	38.2	18.3	22	34.2	29.1	24	8.6%	4.00 [-9.93 , 17.93]
Lahtinen 2004	12.3	16.9	44	18.5	17.7	46	20.1%	-6.20 [-13.35 , 0.95]
Suzuki 2006	29	3.4	24	42.6	6.9	25	33.1%	-13.60 [-16.63 , -10.57]
Yazigi 2012	32	19.5	30	44	19.5	30	14.0%	-12.00 [-21.87 , -2.13]
Total (95% CI)			**147**			**151**	**100.0%**	**-10.64 [-15.27 , -6.00]**

Heterogeneity: Tau² = 14.51; Chi² = 9.43, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 4.50 (P < 0.00001)
Test for subgroup differences: Not applicable



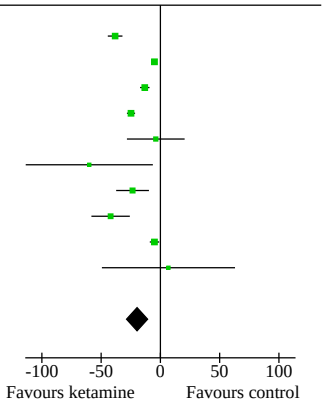
Comparison 6. Perioperative ketamine versus control: major orthopaedic surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Opioid consumption at 24 hours	10	797	Mean Difference (IV, Random, 95% CI)	-19.68 [-28.55, -10.82]
6.2 Opioid consumption at 48 hours	9	557	Mean Difference (IV, Random, 95% CI)	-18.69 [-27.47, -9.90]
6.3 Pain intensity at rest at 24 hours	11	843	Mean Difference (IV, Random, 95% CI)	-6.45 [-9.86, -3.03]
6.4 Pain intensity during movement at 24 hours	4	279	Mean Difference (IV, Random, 95% CI)	-6.73 [-12.64, -0.82]
6.5 Pain intensity at rest at 48 hours	7	453	Mean Difference (IV, Random, 95% CI)	-1.39 [-4.10, 1.32]
6.6 Pain intensity during movement at 48 hours	4	157	Mean Difference (IV, Random, 95% CI)	-7.36 [-13.12, -1.60]

Analysis 6.1. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 1: Opioid consumption at 24 hours

	Ketamine			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cenzig 2014	47	15.3	30	85.2	8.01	30	13.2%	-38.20 [-44.38 , -32.02]	
Dahi-Taleghani 2014	7	2	70	12	3	70	14.1%	-5.00 [-5.84 , -4.16]	
Garg 2016	2.45	2.1	22	15.64	9.31	22	13.7%	-13.19 [-17.18 , -9.20]	
Hadi 2010	35.2	8.9	30	60	2.6	15	13.8%	-24.80 [-28.25 , -21.35]	
Jaksch 2002	40.2	17	15	44.1	45	15	6.8%	-3.90 [-28.24 , 20.44]	
Loftus 2010	142	82	52	202	176	50	2.3%	-60.00 [-113.63 , -6.37]	
Menigaux 2000	26.2	17.9	30	49.7	24.2	15	10.5%	-23.50 [-37.32 , -9.68]	
Nielsen 2017	79	47	74	121	53	73	9.6%	-42.00 [-58.20 , -25.80]	
Remérand 2009	14	13	79	19	12	75	13.7%	-5.00 [-8.95 , -1.05]	
Subramaniam 2011	103.6	87.8	15	96.8	67.85	15	2.1%	6.80 [-49.35 , 62.95]	
Total (95% CI)			**417**			**380**	**100.0%**	**-19.68 [-28.55 , -10.82]**	

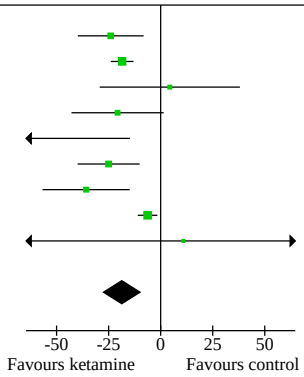
Heterogeneity: Tau² = 144.84; Chi² = 259.65, df = 9 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.35 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	45	20	20	69	30	20	13.7%	-24.00 [-39.80 , -8.20]
Garg 2016	2.59	2	22	21.1	12.9	22	22.4%	-18.51 [-23.96 , -13.06]
Jaksch 2002	63.47	33.22	15	59.08	57.66	15	5.3%	4.39 [-29.29 , 38.07]
Kim 2013	61.9	36.6	35	82.6	39	17	9.6%	-20.70 [-42.85 , 1.45]
Loftus 2010	195	111	52	309	341	50	0.8%	-114.00 [-213.22 , -14.78]
Martinez 2014	52	22	28	77	36	32	14.4%	-25.00 [-39.90 , -10.10]
Menigaux 2000	31.9	22.1	30	67.7	38.3	15	10.3%	-35.80 [-56.73 , -14.87]
Remérand 2009	20.7	14.4	79	27	15.3	75	22.9%	-6.30 [-11.00 , -1.60]
Subramaniam 2011	202.1	164.3	15	191.2	130.95	15	0.7%	10.90 [-95.42 , 117.22]
Total (95% CI)			**296**			**261**	**100.0%**	**-18.69 [-27.47 , -9.90]**

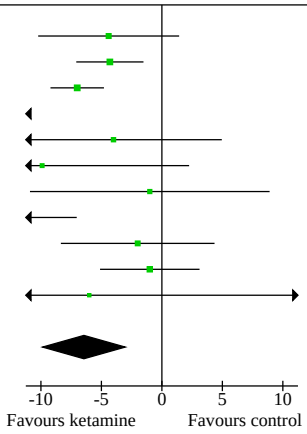
Heterogeneity: Tau² = 81.82; Chi² = 26.24, df = 8 (P = 0.0010); I² = 70%
Test for overall effect: Z = 4.17 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	28.1	9.4	20	32.5	9.4	20	10.4%	-4.40 [-10.23 , 1.43]
Cenzig 2014	2	4.8	30	6.3	6.1	30	13.5%	-4.30 [-7.08 , -1.52]
Dahi-Taleghani 2014	10	5	70	17	8	70	14.0%	-7.00 [-9.21 , -4.79]
Hadi 2013	40	7	30	56	5.1	15	12.8%	-16.00 [-19.60 , -12.40]
Jaksch 2002	10	12	15	14	13	15	7.4%	-4.00 [-12.95 , 4.95]
Kim 2013	36.1	16	35	46	23	17	5.2%	-9.90 [-22.05 , 2.25]
Loftus 2010	47	27	52	48	24	50	6.6%	-1.00 [-10.90 , 8.90]
Menigaux 2000	24.7	11.7	30	42.6	19.8	15	5.9%	-17.90 [-28.76 , -7.04]
Nielsen 2017	46	19	73	48	20	72	9.8%	-2.00 [-8.35 , 4.35]
Remérand 2009	14	14	79	15	12	75	12.2%	-1.00 [-5.11 , 3.11]
Subramaniam 2011	47	28	15	53	30	15	2.3%	-6.00 [-26.77 , 14.77]
Total (95% CI)			**449**			**394**	**100.0%**	**-6.45 [-9.86 , -3.03]**

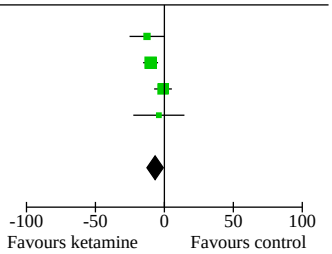
Heterogeneity: Tau² = 20.45; Chi² = 44.68, df = 10 (P < 0.00001); I² = 78%
Test for overall effect: Z = 3.70 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 4: Pain intensity during movement at 24 hours

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kim 2013	45.4	19.2	35	58	23	17	16.0%	-12.60 [-25.25 , 0.05]
Menigaux 2000	48	10	30	58	8	15	40.1%	-10.00 [-15.40 , -4.60]
Nielsen 2017	63	21	72	64	18	70	35.2%	-1.00 [-7.43 , 5.43]
Subramaniam 2011	65	23	25	69	32	15	8.7%	-4.00 [-22.53 , 14.53]
Total (95% CI)			**162**			**117**	**100.0%**	**-6.73 [-12.64 , -0.82]**

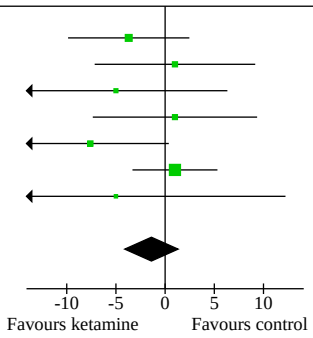
Heterogeneity: Tau² = 15.09; Chi² = 5.37, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 5: Pain intensity at rest at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adam 2005	16.3	11.9	20	20	7.5	20	19.3%	-3.70 [-9.86 , 2.46]
Jaksch 2002	7	14	15	6	8	15	11.0%	1.00 [-7.16 , 9.16]
Kim 2013	29	18.6	35	34	20	17	5.7%	-5.00 [-16.33 , 6.33]
Loftus 2010	54	21	52	53	22	50	10.5%	1.00 [-7.35 , 9.35]
Menigaux 2000	16.7	12.8	30	24.3	12.9	15	11.5%	-7.60 [-15.57 , 0.37]
Remérand 2009	15	16	79	14	11	75	39.4%	1.00 [-3.32 , 5.32]
Subramaniam 2011	43	22	15	48	26	15	2.5%	-5.00 [-22.24 , 12.24]
Total (95% CI)			**246**			**207**	**100.0%**	**-1.39 [-4.10 , 1.32]**

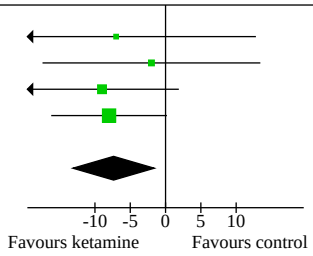
Heterogeneity: Tau² = 0.00; Chi² = 5.25, df = 6 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Perioperative ketamine versus control: major orthopaedic surgery, Outcome 6: Pain intensity during movement at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Subramaniam 2011	63	21	15	70	33	15	8.5%	-7.00 [-26.79 , 12.79]
Jaksch 2002	21	20	15	23	23	15	14.0%	-2.00 [-17.42 , 13.42]
Kim 2013	36	18.3	35	45	19	17	28.1%	-9.00 [-19.88 , 1.88]
Menigaux 2000	28	18	30	36	10	15	49.5%	-8.00 [-16.19 , 0.19]
Total (95% CI)			**95**			**62**	**100.0%**	**-7.36 [-13.12 , -1.60]**

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



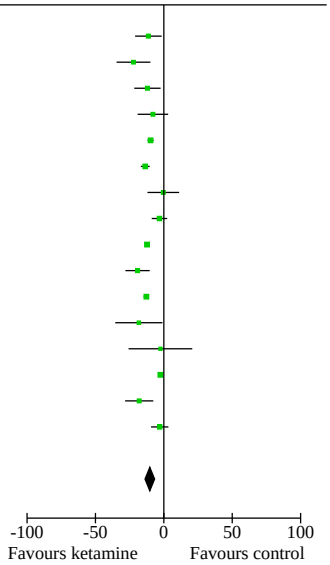
Comparison 7. Perioperative ketamine versus control: major abdominal surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Opioid consumption at 24 hours	16	1029	Mean Difference (IV, Random, 95% CI)	-10.26 [-13.75, -6.76]
7.2 Opioid consumption at 48 hours	10	704	Mean Difference (IV, Random, 95% CI)	-14.34 [-21.21, -7.48]
7.3 Pain intensity at rest at 24 hours	18	1178	Mean Difference (IV, Random, 95% CI)	-7.42 [-10.63, -4.21]
7.4 Pain intensity during movement at 24 hours	9	666	Mean Difference (IV, Random, 95% CI)	-2.80 [-11.24, 5.65]
7.5 Pain intensity at rest at 48 hours	13	891	Mean Difference (IV, Random, 95% CI)	-5.99 [-8.89, -3.08]
7.6 Pain intensity during movement at 48 hours	9	662	Mean Difference (IV, Random, 95% CI)	-2.91 [-9.15, 3.34]

Analysis 7.1. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	19.4	10.7	15	30.7	15.9	15	5.4%	-11.30 [-21.00 , -1.60]
Guignard 2002	42.7	16.3	25	64.9	27	25	4.3%	-22.20 [-34.56 , -9.84]
Guillou 2003	36	26	41	48	20	52	5.4%	-12.00 [-21.64 , -2.36]
Ilkjaer 1998	28	21	30	36	23	30	4.8%	-8.00 [-19.14 , 3.14]
Kafali 2004	44.2	4.6	30	53.9	4	30	9.0%	-9.70 [-11.88 , -7.52]
Kamal 2008	33.3	7.4	40	46.9	7.4	40	8.6%	-13.60 [-16.84 , -10.36]
Katz 2004	51.9	33.3	97	52.3	32.8	46	4.6%	-0.40 [-11.97 , 11.17]
Lehmann 2001	17.5	11.3	40	20.7	14.3	40	7.5%	-3.20 [-8.85 , 2.45]
Parikh 2011	5.8	1.48	30	18.1	1.8	30	9.3%	-12.30 [-13.13 , -11.47]
Roytblat 1993	29.5	7.5	11	48.7	13	11	5.8%	-19.20 [-28.07 , -10.33]
Safavi 2011	2.33	0.6	30	15.1	5.3	30	9.1%	-12.77 [-14.68 , -10.86]
Snijdelaar 2004	32.15	18.6	13	50.42	24.7	12	2.8%	-18.27 [-35.52 , -1.02]
Stubhaug 1997	65.5	22.6	10	68	30	10	1.8%	-2.50 [-25.78 , 20.78]
Ünlügenc 2003	46.5	1.7	30	49	1.6	28	9.3%	-2.50 [-3.35 , -1.65]
Webb 2007	25.3	23.3	52	43.3	31.9	59	5.1%	-18.00 [-28.31 , -7.69]
Zakine 2008	22.3	15.1	50	25.3	12.6	27	7.1%	-3.00 [-9.33 , 3.33]
Total (95% CI)			**544**			**485**	**100.0%**	**-10.26 [-13.75 , -6.76]**

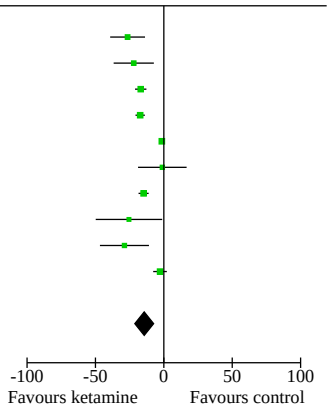
Heterogeneity: Tau² = 34.08; Chi² = 324.55, df = 15 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.76 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	27.6	12.4	15	54.1	21.9	15	9.1%	-26.50 [-39.24 , -13.76]
Guillou 2003	58	35	41	80	37	52	8.2%	-22.00 [-36.69 , -7.31]
Kafali 2004	69.8	8	30	86.7	8.4	30	12.6%	-16.90 [-21.05 , -12.75]
Kamal 2008	66.7	4.9	40	84	9.9	40	12.8%	-17.30 [-20.72 , -13.88]
Kararmaz 2003	6.06	1.38	20	7.52	2	20	13.2%	-1.46 [-2.52 , -0.40]
Katz 2004	81	51.6	97	82.1	50.1	46	7.0%	-1.10 [-18.85 , 16.65]
Lak 2010	3	2	25	17.8	9.2	25	12.7%	-14.80 [-18.49 , -11.11]
Snijdelaar 2004	47.9	26.2	13	73.4	34.8	12	5.0%	-25.50 [-49.80 , -1.20]
Webb 2007	44.1	41.2	50	72.9	52.7	56	7.0%	-28.80 [-46.71 , -10.89]
Zakine 2008	9.5	10.5	50	12.3	10.7	27	12.4%	-2.80 [-7.78 , 2.18]
Total (95% CI)			**381**			**323**	**100.0%**	**-14.34 [-21.21 , -7.48]**

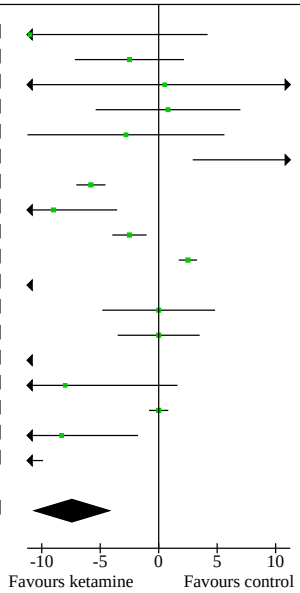
Heterogeneity: Tau² = 92.66; Chi² = 176.59, df = 9 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.10 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	25	18	15	36	24	15	2.8%	-11.00 [-26.18 , 4.18]
Bornemann-Cimenti 2016	17.5	7.2	37	20	9	19	6.3%	-2.50 [-7.16 , 2.16]
Chen 2004	29.4	21.4	20	28.9	20.7	20	3.3%	0.50 [-12.55 , 13.55]
De Kock 2001	18.8	9.8	40	18	12.3	20	5.7%	0.80 [-5.39 , 6.99]
Guillou 2003	21.8	21.8	41	24.6	18.9	52	4.8%	-2.80 [-11.22 , 5.62]
Joly 2005	40.7	19.5	24	27.7	16.3	25	4.2%	13.00 [2.92 , 23.08]
Kafali 2004	11.3	2.7	30	17.1	2.2	30	7.2%	-5.80 [-7.05 , -4.55]
Kakinohana 2004	6	7	25	15	12	25	6.0%	-9.00 [-14.45 , -3.55]
Kamal 2008	26	2.5	40	28.5	4	40	7.1%	-2.50 [-3.96 , -1.04]
Katz 2004	19.4	2.8	97	16.9	1.9	46	7.2%	2.50 [1.72 , 3.28]
Lak 2010	32.8	14	25	65.6	13.6	25	5.1%	-32.80 [-40.45 , -25.15]
Lehmann 2001	11	11	40	11	11	40	6.2%	0.00 [-4.82 , 4.82]
Parikh 2011	21.4	2.4	30	21.4	9.5	30	6.7%	0.00 [-3.51 , 3.51]
Safavi 2011	0.7	1.3	30	59	20	30	5.3%	-58.30 [-65.47 , -51.13]
Snijdelaar 2004	12	10	13	20	14	12	4.4%	-8.00 [-17.61 , 1.61]
Ünlügenc 2003	10	1	30	10	2	28	7.2%	0.00 [-0.82 , 0.82]
Webb 2007	15.6	16.1	50	23.9	18.4	57	5.6%	-8.30 [-14.84 , -1.76]
Zakine 2008	16.7	15.9	50	35	19	27	4.8%	-18.30 [-26.71 , -9.89]
Total (95% CI)			**637**			**541**	**100.0%**	**-7.42 [-10.63 , -4.21]**

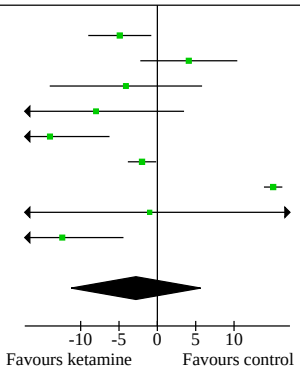
Heterogeneity: Tau² = 37.00; Chi² = 495.89, df = 17 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.53 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 4: Pain intensity during movement at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bornemann-Cimenti 2016	30.1	8.2	37	35	7	19	12.2%	-4.90 [-9.01 , -0.79]
De Kock 2001	33	13.2	40	28.9	11	20	11.8%	4.10 [-2.22 , 10.42]
Guillou 2003	37.1	26.8	41	41.2	20.6	52	10.7%	-4.10 [-14.03 , 5.83]
Joly 2005	36	20	24	44	21	25	10.2%	-8.00 [-19.48 , 3.48]
Kakinohana 2004	30	14	25	44	14	25	11.4%	-14.00 [-21.76 , -6.24]
Kamal 2008	38	3.9	40	40	4.5	40	12.5%	-2.00 [-3.85 , -0.15]
Katz 2004	55.7	2.4	97	40.6	3.8	46	12.5%	15.10 [13.90 , 16.30]
Snijdelaar 2004	27	25	13	28	26	12	7.4%	-1.00 [-21.03 , 19.03]
Webb 2007	38.7	22.2	51	51.1	20.2	59	11.3%	-12.40 [-20.38 , -4.42]
Total (95% CI)			**368**			**298**	**100.0%**	**-2.80 [-11.24 , 5.65]**

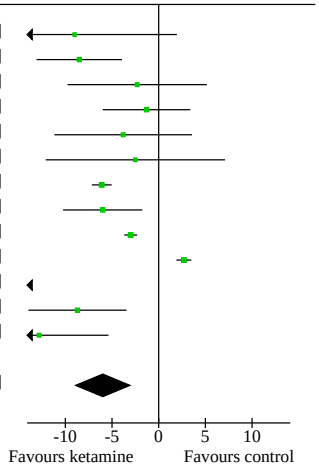
Heterogeneity: Tau² = 147.50; Chi² = 356.93, df = 8 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 5: Pain intensity at rest at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adriaenssens 1999	12	12	15	21	18	15	4.2%	-9.00 [-19.95 , 1.95]
Bornemann-Cimenti 2016	10.5	6.6	37	19	9	19	8.4%	-8.50 [-13.07 , -3.93]
Chen 2004	23.9	14.4	20	26.2	9.1	20	6.2%	-2.30 [-9.77 , 5.17]
De Kock 2001	15.1	9	40	16.4	8.6	20	8.3%	-1.30 [-5.99 , 3.39]
Guillou 2003	15.1	18	41	18.9	18	52	6.3%	-3.80 [-11.17 , 3.57]
Joly 2005	26	13	24	28.5	20.6	25	4.9%	-2.50 [-12.11 , 7.11]
Kafali 2004	6	2.1	30	12.1	2.1	30	10.4%	-6.10 [-7.16 , -5.04]
Kakinohana 2004	4	6	25	10	9	25	8.6%	-6.00 [-10.24 , -1.76]
Kamal 2008	19	1	40	22	2	40	10.5%	-3.00 [-3.69 , -2.31]
Katz 2004	14	2.9	97	11.3	1.9	46	10.5%	2.70 [1.90 , 3.50]
Lak 2010	24.8	10.4	25	46	9.6	25	7.6%	-21.20 [-26.75 , -15.65]
Webb 2007	9.7	10.3	51	18.4	16.3	52	7.8%	-8.70 [-13.96 , -3.44]
Zakine 2008	12.2	13.5	50	25	17	27	6.2%	-12.80 [-20.22 , -5.38]
Total (95% CI)			**495**			**396**	**100.0%**	**-5.99 [-8.89 , -3.08]**

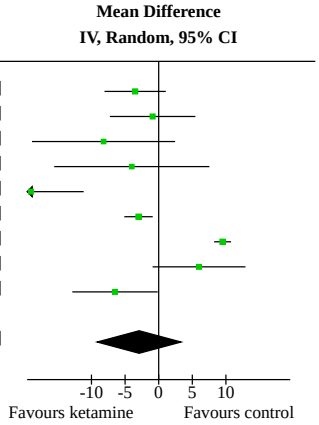
Heterogeneity: Tau² = 20.79; Chi² = 272.38, df = 12 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.04 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7: Perioperative ketamine versus control: major abdominal surgery, Outcome 6: Pain intensity during movement at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bornemann-Cimenti 2016	27.5	6.5	37	31	9	19	12.0%	-3.50 [-8.06 , 1.06]
De Kock 2001	28	13.4	40	28.9	11	20	11.3%	-0.90 [-7.26 , 5.46]
Guillou 2003	26.8	26.8	41	35	24.7	51	9.3%	-8.20 [-18.84 , 2.44]
Joly 2005	33	18	24	37	23	25	8.9%	-4.00 [-15.54 , 7.54]
Kakinohana 2004	23	12	25	42	16	25	10.7%	-19.00 [-26.84 , -11.16]
Kamal 2008	32	4.49	40	35	5.13	40	12.6%	-3.00 [-5.11 , -0.89]
Katz 2004	47.2	3.1	97	37.7	3.8	46	12.7%	9.50 [8.24 , 10.76]
Snijdelaar 2004	11	12	13	5	4	12	11.1%	6.00 [-0.90 , 12.90]
Webb 2007	32.9	16.4	51	39.4	17.1	56	11.3%	-6.50 [-12.85 , -0.15]
Total (95% CI)			**368**			**294**	**100.0%**	**-2.91 [-9.15 , 3.34]**

Heterogeneity: Tau² = 79.20; Chi² = 177.25, df = 8 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



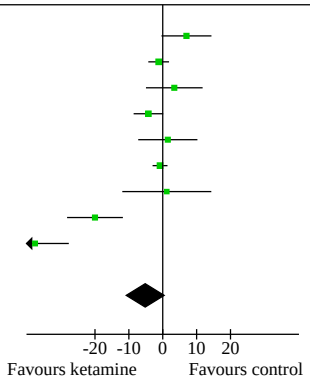
Comparison 8. Perioperative ketamine versus control: total abdominal hysterectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Opioid consumption at 24 hours	9	511	Mean Difference (IV, Random, 95% CI)	-5.18 [-10.77, 0.41]
8.2 Opioid consumption at 48 hours	5	378	Mean Difference (IV, Random, 95% CI)	-15.32 [-33.20, 2.56]
8.3 Pain intensity at rest at 24 hours	8	493	Mean Difference (IV, Random, 95% CI)	-2.58 [-4.64, -0.52]

Analysis 8.1. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aubrun 2008	24.8	19.2	45	17.8	16.4	45	11.2%	7.00 [-0.38 , 14.38]
Dahl 2000	19.2	6.3	29	20.4	8	60	13.3%	-1.20 [-4.26 , 1.86]
Garcia-Navia 2016	30.95	7.88	11	27.54	11.75	11	10.6%	3.41 [-4.95 , 11.77]
Gilabert Morell 2002	11.4	6.7	44	15.63	9.31	22	12.8%	-4.23 [-8.60 , 0.14]
Hercock 1999	34.5	15.2	24	33	16	25	10.4%	1.50 [-7.24 , 10.24]
Karaman 2006	13.8	4.1	40	14.6	4.1	20	13.6%	-0.80 [-3.00 , 1.40]
Murdoch 2002	67.6	25.1	21	66.4	17.7	21	7.9%	1.20 [-11.94 , 14.34]
Sen 2009	28	8	20	48	17	20	10.7%	-20.00 [-28.23 , -11.77]
Yalcin 2012	35.34	13.71	26	73.03	22.41	27	9.6%	-37.69 [-47.65 , -27.73]
Total (95% CI)			**260**			**251**	**100.0%**	**-5.18 [-10.77 , 0.41]**

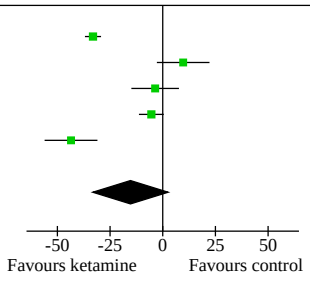
Heterogeneity: Tau² = 58.65; Chi² = 78.16, df = 8 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Arikan 2016	32.6	9.2	40	65.7	8.2	40	21.1%	-33.10 [-36.92 , -29.28]
Aubrun 2008	59.6	31.1	45	49.9	29.3	45	19.3%	9.70 [-2.78 , 22.18]
Dahl 2000	40.3	23.4	60	43.9	26.4	29	19.6%	-3.60 [-14.89 , 7.69]
Gilabert Morell 2002	17.2	8.6	44	22.6	12.72	22	20.8%	-5.40 [-11.29 , 0.49]
Yalcin 2012	42.52	15.08	26	86.05	29.46	27	19.3%	-43.53 [-56.06 , -31.00]
Total (95% CI)			**215**			**163**	**100.0%**	**-15.32 [-33.20 , 2.56]**

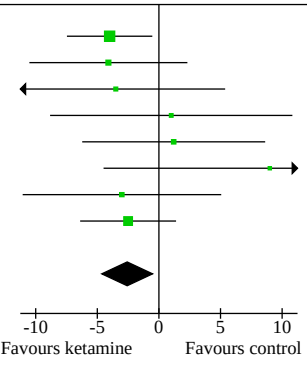
Heterogeneity: Tau² = 391.26; Chi² = 109.09, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Perioperative ketamine versus control: total abdominal hysterectomy, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Arikan 2016	27	5	40	31	10	40	35.3%	-4.00 [-7.46 , -0.54]
Aubrun 2008	15.2	11.8	45	19.3	18.5	45	10.3%	-4.10 [-10.51 , 2.31]
Dahl 2000	54.5	22	60	58	19	29	5.4%	-3.50 [-12.38 , 5.38]
Grady 2012	37	22	30	36	17	32	4.4%	1.00 [-8.83 , 10.83]
Hercock 1999	14	12.5	24	12.8	14	25	7.7%	1.20 [-6.22 , 8.62]
Lo 2008	41	20.2	15	32	17.4	15	2.3%	9.00 [-4.49 , 22.49]
Sen 2009	10	13	20	13	13	20	6.5%	-3.00 [-11.06 , 5.06]
Yalcin 2012	2.5	2.5	26	5	10	27	28.0%	-2.50 [-6.39 , 1.39]
Total (95% CI)			**260**			**233**	**100.0%**	**-2.58 [-4.64 , -0.52]**

Heterogeneity: Tau² = 0.00; Chi² = 5.25, df = 7 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable



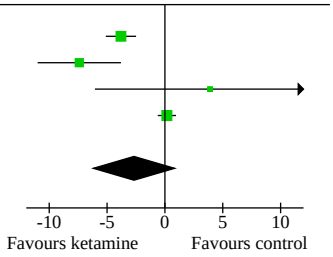
Comparison 9. Perioperative ketamine versus control: laparoscopic procedures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Opioid consumption at 24 hours	4	199	Mean Difference (IV, Random, 95% CI)	-2.67 [-6.19, 0.84]
9.2 Opioid consumption at 48 hours	2	85	Mean Difference (IV, Random, 95% CI)	-4.47 [-12.21, 3.27]
9.3 Pain intensity at rest at 24 hours	9	484	Mean Difference (IV, Random, 95% CI)	-2.32 [-6.65, 2.02]

Analysis 9.1. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 1: Opioid consumption at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ayoglu 2005	19.7	1.9	20	23.5	2.3	20	32.4%	-3.80 [-5.11 , -2.49]
Hasanein 2011	40	6.1	30	47.4	8	30	25.0%	-7.40 [-11.00 , -3.80]
Leal 2013	29	18.4	20	25.1	13.3	20	9.1%	3.90 [-6.05 , 13.85]
Lin 2016	5.42	1.64	30	5.25	1.45	29	33.4%	0.17 [-0.62 , 0.96]
Total (95% CI)			**100**			**99**	**100.0%**	**-2.67 [-6.19 , 0.84]**

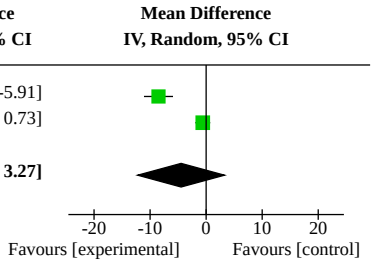
Heterogeneity: Tau² = 9.45; Chi² = 39.06, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 2: Opioid consumption at 48 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Choi 2015	22.5	3.8	25	31	5.4	25	49.0%	-8.50 [-11.09 , -5.91]
Papaziogas 2001	0.3	1.15	18	0.9	2.56	17	51.0%	-0.60 [-1.93 , 0.73]
Total (95% CI)			**43**			**42**	**100.0%**	**-4.47 [-12.21 , 3.27]**

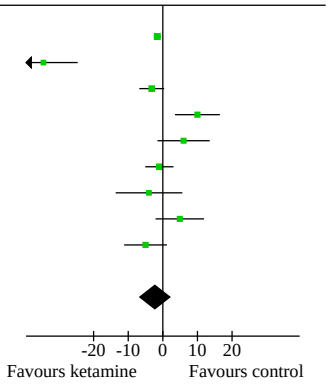
Heterogeneity: Tau² = 30.10; Chi² = 28.33, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9: Perioperative ketamine versus control: laparoscopic procedures, Outcome 3: Pain intensity at rest at 24 hours

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ayoglu 2005	3.2	1.6	20	4.8	1.6	20	14.4%	-1.60 [-2.59 , -0.61]
Karcioglu 2013	13.5	11.2	17	48	19	20	8.3%	-34.50 [-44.38 , -24.62]
Kwok 2004	12.4	12.5	90	15.6	8.5	45	13.2%	-3.20 [-6.78 , 0.38]
Leal 2013	15	13	20	5	7	20	11.0%	10.00 [3.53 , 16.47]
Leal 2015	14	15	20	8	10	28	10.1%	6.00 [-1.55 , 13.55]
Lin 2016	24	8	30	25	8	29	12.9%	-1.00 [-5.08 , 3.08]
Mathisen 1999	20	14	32	24	18	18	8.5%	-4.00 [-13.63 , 5.63]
Nesek-Adam 2012	23.3	11.3	20	18.4	11.3	20	10.5%	4.90 [-2.10 , 11.90]
Papaziogas 2001	0.0001	0.0001	18	5	13	17	11.2%	-5.00 [-11.18 , 1.18]
Total (95% CI)			**267**			**217**	**100.0%**	**-2.32 [-6.65 , 2.02]**

Heterogeneity: Tau² = 33.64; Chi² = 64.37, df = 8 (P < 0.00001); I² = 88%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL (via CRSO)

1. MESH DESCRIPTOR Ketamine EXPLODE ALL TREES

2. ((ketamine or ketalar or calipsol or ketanest or ketaset or calypsol or kalipsol or ci-581)):TI,AB,KY

3. #1 OR #2

4. MESH DESCRIPTOR Pain, Postoperative

5. ((postoperat* adj3 pain*)):TI,AB,KY

6. (pain* following surg*):TI,AB,KY

7. (pain* following treat*):TI,AB,KY

8. (pain* following operation*):TI,AB,KY

9. (post-operat* pain):TI,AB,KY

10. (((post adj1 surg*) or postsurg* or post-surg*)):TI,AB,KY

11. (((post adj1 operat*) or postoperat* or post-operat*)):TI,AB,KY

12. pain*:TI,AB,KY

13. #10 OR #11

14. #12 AND #13

15. (((post-operat* or postoperat* or post-surg* or postsurg*) adj analgesi*)):TI,AB,KY

16. (analgesi* following surg*):TI,AB,KY

17. (analgesi* following operat*):TI,AB,KY

18. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #14 OR

19. #15 OR #16 OR #17

20. #3 AND #18

Appendix 2. MEDLINE (via Ovid)

1. Ketamine/

2. (ketamine or ketalar or calipsol or ketanest or ketaset or calypsol or kalipsol or ci-581).tw.

3. or/1-2

4. Pain, Postoperative/

5. (postoperat* adj3 pain*).tw.

6. pain* following surg*.tw.

7. pain* following treat*.tw.

8. pain* following operation*.tw.

9. post-operat* pain.tw.

10. ((post adj1 surg*) or postsurg* or post-surg*).tw.

11. ((post adj1 operat*) or postoperat* or post-operat*).tw.

12. pain*.tw.

13. (10 or 11) and 12

14. ((post-operat* or postoperat* or post-surg* or postsurg*) adj analgesi*).tw.

15. analgesi* following surg*.tw.

16. analgesi* following operat*.tw.

17. 4 or 5 or 6 or 7 or 8 or 9 or 13 or 14 or 15 or 16

18. 3 and 17

19. randomized controlled trial.pt.

20. controlled clinical trial.pt.

21. randomized.ab.

22. placebo.ab.

23. drug therapy.fs.

24. randomly.ab.

25. trial.ab.

26. or/19-25

27. exp animals/ not humans.sh.

28. 26 not 27

29. 18 and 28

Appendix 3. Embase (via Ovid)

1. Ketamine/

2. (ketamine or ketalar or calipsol or ketanest or ketaset or calypsol or kalipsol or ci-581).tw.

3. or/1-2

4. Pain, Postoperative/

5. (postoperat* adj3 pain*).tw.

6. pain* following surg*.tw.

7. pain* following treat*.tw.

8. pain* following operation*.tw.

9. post-operat* pain.tw.

10. ((post adj1 surg*) or postsurg* or post-surg*).tw.

11. ((post adj1 operat*) or postoperat* or post-operat*).tw.

12. pain*.tw.

13. (10 or 11) and 12

14. ((post-operat* or postoperat* or post-surg* or postsurg*) adj analgesi*).tw.

15. analgesi* following surg*.tw.

16. analgesi* following operat*.tw.

17. 4 or 5 or 6 or 7 or 8 or 9 or 13 or 14 or 15 or 16

18. 3 and 17

19. random$.tw.

20. factorial$.tw.

21. crossover$.tw.

22. cross over$.tw.

23. cross-over$.tw.

24. placebo$.tw.

25. (doubl$ adj blind$).tw.

26. (singl$ adj blind$).tw.

27. assign$.tw.

28. allocat$.tw.

29. volunteer$.tw.

30. Crossover Procedure/

31. double-blind procedure.tw.

32. Randomized Controlled Trial/

33. Single Blind Procedure/

34. or/19-33

35. (animal/ or nonhuman/) not human/

36. 34 not 35

37. 18 and 36

Appendix 4. Postoperative opioid consumption in different types of surgery

24-hour outcomes

24-hour opioid consumption after thoracotomy

Four studies assessed opioid consumption during the first 24 hours after thoracotomy; 120 participants received ketamine and 121 participants served as controls (Argiriadou 2011; Dualé 2009; Michelet 2007; Ysasi 2010). Participants who received ketamine consumed 6 mg less opioid (95% CI -10.3 to -1.4), compared to participants who received control treatment (Analysis 5.1). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

24-hour opioid consumption after major orthopaedic surgery

Ten studies provided data for 24-hour opioid consumption after major orthopaedic surgery; 417 participants received ketamine and 380 participants received control treatment (Cenzig 2014; Dahi-Taleghani 2014; Garg 2016; Hadi 2010; Jaksch 2002; Loftus 2010; Menigaux 2000; Nielsen 2017; Remérand 2009; Subramaniam 2011). Participants who had received ketamine consumed 20 mg less opioid (95% CI -28.6 to -10.8), compared to controls (Analysis 6.1). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

24-hour opioid consumption after major abdominal surgery

Sixteen studies gave data of pain intensity at rest at 24 hours after major abdominal surgery; 544 participants received ketamine and 485 participants received control treatment (Adriaenssens 1999; Guignard 2002; Guillou 2003; Ilkjaer 1998; Kafali 2004; Kamal 2008; Katz 2004; Lehmann 2001; Parikh 2011; Roytblat 1993; Safavi 2011; Snijdelaar 2004; Stubhaug 1997; Webb 2007; Zakine 2008; Ünlügenc 2003). Ketamine treatment reduced opioid consumption by 10 mg of morphine equivalents (95% CI -13.8 to -6.8; Analysis 7.1). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

24-hour opioid consumption after total abdominal hysterectomy

Nine studies provided data for 24-hour opioid consumption after total abdominal hysterectomy; 260 participants received ketamine and 251 participants received control treatment (Aubrun 2008; Dahl 2000; Garcia-Navia 2016; Gilabert Morell 2002; Hercock 1999; Karaman 2006; Murdoch 2002; Sen 2009; Yalcin 2012). Ketamine administration reduced 24-hour opioid consumption after total abdominal hysterectomy by 5 mg of morphine equivalents (95% CI -10.8 to 0.4; Analysis 8.1). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

24-hour opioid consumption after laparoscopic procedures

Four studies assessed 24-hour opioid consumption after laparoscopic procedures; 100 participants were given ketamine and 99 participants served as controls (Ayoglu 2005; Hasanein 2011; Leal 2013; Lin 2016). Ketamine treatment reduced 24-hour opioid consumption after laparoscopic procedures by 3 mg of morphine equivalents (95% CI -6.2 to 0.8; Analysis 9.1). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

48-hour outcomes

48-hour opioid consumption after thoracotomy

Three studies provided data of 48-hour opioid consumption after thoracotomy; 95 participants received ketamine and 96 participants served as controls (Argiriadou 2011; Lahtinen 2004; Michelet 2007). Ketamine treatment reduced 48-hour opioid consumption after thoracotomy by 13 mg (95% CI -18.3 to -6.7; Analysis 5.2). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

48-hour opioid consumption after major orthopaedic surgery

Nine studies assessed 48-hour opioid consumption after major orthopaedic surgery; 296 participants received ketamine and 261 participants received control treatment (Adam 2005; Garg 2016; Jaksch 2002; Kim 2013; Loftus 2010; Martinez 2014; Menigaux 2000; Remérand 2009; Subramaniam 2011). Participants who had received ketamine consumed 19 mg less opioid (95% CI -27.5 to -9.9), compared to participants who received control treatment (Analysis 6.2). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

48-hour opioid consumption after major abdominal surgery

Ten studies assessed 48-hour opioid consumption after major abdominal surgery; 381 participants received ketamine and 323 participants received control treatment (Adriaenssens 1999; Guillou 2003; Kafali 2004; Kamal 2008; Kararmaz 2003; Katz 2004; Lak 2010; Snijdelaar 2004; Webb 2007; Zakine 2008). Ketamine treatment reduced 48-hour opioid consumption by 14 mg of morphine equivalents (95% CI -21.2 to

-7.5), after major abdominal surgery (Analysis 7.2). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

48-hour opioid consumption after total abdominal hysterectomy

Five studies provided data on 48-hour opioid consumption after total abdominal hysterectomy; 215 participants received ketamine and 163 participants served as controls (Arikan 2016; Aubrun 2008; Dahl 2000; Gilabert Morell 2002; Yalcin 2012). Treatment with ketamine reduced 48 hour postoperative opioid consumption by 15 milligrams of morphine equivalents (95% CI -33.2 to 2.6; Analysis 8.2). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

48-hour opioid consumption after laparoscopic procedures

Two studies investigated ketamine's effect on 48-hour opioid consumption after laparoscopic procedures; 43 participants received ketamine and 42 participants received control treatment (Choi 2015; Papaziogas 2001). Ketamine treatment reduced 48-hour opioid consumption by 5 mg (95% CI -12.2 to 3.3; Analysis 9.2). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

Appendix 5. Postoperative pain in different types of surgery

Pain intensity at rest at 24 hours after thoracotomy

Thirteen studies assessed pain at 24 hours at rest after thoracotomy; 388 participants received ketamine and 394 participants received control treatment (Argiriadou 2011; D'Alonzo 2011; Dualé 2009; Fiorelli 2015; Joseph 2012; Lahtinen 2004; Mendola 2012; Michelet 2007; Patel 2016; Suzuki 2006; Tena 2014; Yazigi 2012; Ysasi 2010). Visual analogue scale (VAS) scores were 4 mm lower (95% CI -8.8 to 1), among participants who received ketamine (Analysis 5.3). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 24 hours after thoracotomy

Five studies assessed postoperative pain intensity at 24 hours on movement after thoracotomy (Argiriadou 2011; Joseph 2012 Lahtinen 2004; Tena 2014; Yazigi 2012). VAS scores were 7 mm lower (95% CI -20.1 to 5.5), among 154 participants who received ketamine versus 161 participants who received control treatment (Analysis 5.4). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

Pain intensity at rest at 48 hours after thoracotomy

Nine studies provided data of pain intensity at rest at 48 hours after thoracotomy (Argiriadou 2011; Chazan 2010; Fiorelli 2015; Joseph 2012; Lahtinen 2004; Mendola 2012; Michelet 2007; Suzuki 2006; Yazigi 2012). VAS scores were 7 mm lower (95% CI -10.4 to -3.4), among 265 participants who received ketamine versus 265 participants who served as controls (Analysis 5.5). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 48 hours after thoracotomy

Five studies assessed pain intensity at 48 hours during movement after thoracotomy (Argiriadou 2011; Joseph 2012; Lahtinen 2004; Suzuki 2006; Yazigi 2012). VAS scores were 11 mm lower (95% CI -15.3 to -6), among 147 participants who received ketamine versus 151 participants who received control treatment (Analysis 5.6). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

Pain intensity at rest at 24 hours after major orthopaedic surgery

Eleven studies assessed pain intensity at rest at 24 hours after major orthopaedic surgery; 449 participants received ketamine and 394 participants received control treatment (Adam 2005; Cenzig 2014; Dahi-Taleghani 2014; Hadi 2013; Jaksch 2002; Kim 2013; Loftus 2010; Menigaux 2000; Nielsen 2017; Remérand 2009; Subramaniam 2011). VAS scores were 7 mm lower (95% CI -9.9 to -3.0) after ketamine treatment compared to those who received control treatment (Analysis 6.3). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 24 hours after major orthopaedic surgery

Four studies gave data about pain intensity at 24 hours during movement after major orthopaedic surgery; 162 participants who received ketamine had 7 mm lower VAS scores (95% CI -12.6 to -0.8), compared to 117 participants who received control treatment (Kim 2013; Menigaux 2000; Nielsen 2017; Subramaniam 2011; Analysis 6.4). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

Pain intensity at rest at 48 hours after major orthopaedic surgery

Seven studies assessed pain intensity at rest at 48 hours after major orthopaedic surgery; 246 participants received ketamine and 207 participants served as controls (Adam 2005; Jaksch 2002; Kim 2013; Loftus 2010; Menigaux 2000; Remérand 2009; Subramaniam 2011). VAS scores were 1 mm lower (95% CI -4.1 to 1.3), after ketamine treatment (Analysis 6.5). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 48 hours after major orthopaedic surgery

Four studies provided data of pain intensity at 48 hours during movement after major orthopaedic surgery; 95 participants experienced 7 mm lower VAS scores (95% CI -13.1 to -1.6) after ketamine treatment compared to 62 participants who served as controls (Jaksch 2002; Kim 2013; Menigaux 2000; Subramaniam 2011; Analysis 6.6). We assessed the quality of evidence for this outcome as very low. We downgraded the evidence three times because there were fewer than 400 participants in the analysis.

Pain intensity at rest at 24 hours after major abdominal surgery

Eighteen studies gave data of pain intensity at rest at 24 hours after major abdominal surgery; 637 participants received ketamine and 541 participants received control treatment (Adriaenssens 1999; Bornemann-Cimenti 2016; Chen 2004; De Kock 2001; Guillou 2003; Joly 2005; Kafali 2004; Kakinohana 2004; Kamal 2008; Katz 2004; Lak 2010; Lehmann 2001; Parikh 2011; Safavi 2011; Snijdelaar 2004; Webb 2007; Zakine 2008; Ünlügenc 2003). VAS scores were 7 mm lower (95% CI -10.6 to -4.2), after ketamine treatment compared to controls (Analysis 7.3). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 24 hours after major abdominal surgery

Nine studies assessed pain intensity at 24 hours during movement after major abdominal surgery (Bornemann-Cimenti 2016; De Kock 2001; Guillou 2003; Joly 2005; Kakinohana 2004; Kamal 2008; Katz 2004; Snijdelaar 2004; Webb 2007). VAS scores were 3 mm lower (95% CI -11.2 to 5.7), among 368 participants who received ketamine compared to 298 participants who served as controls (Analysis 7.4). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity at rest at 48 hours after major abdominal surgery

Thirteen studies provided data of pain intensity at rest at 48 hours after major abdominal surgery; 495 participants received ketamine and 396 participants received control treatment (Adriaenssens 1999; Bornemann-Cimenti 2016; Chen 2004; De Kock 2001; Guillou 2003; Joly 2005; Kafali 2004; Kakinohana 2004; Kamal 2008; Katz 2004; Lak 2010; Webb 2007; Zakine 2008). VAS scores were 6 mm lower (95% CI -8.9 to -3.1), after ketamine treatment compared to those who received control treatment (Analysis 7.5). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 48 hours after major abdominal surgery

Nine studies assessed pain intensity at 48 hours during movement after major abdominal surgery (Bornemann-Cimenti 2016; De Kock 2001; Guillou 2003; Joly 2005; Kakinohana 2004; Kamal 2008; Katz 2004; Snijdelaar 2004; Webb 2007). VAS scores were 3 mm lower (95% CI -9.2 to 3.3), after ketamine treatment among 368 participants versus 294 participants who received control treatment (Analysis 7.6). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity at rest at 24 hours after total abdominal hysterectomy

Eight studies provided data for pain intensity at rest at 24 hours after total abdominal hysterectomy; 260 participants received ketamine and 233 participants received control treatment (Arikan 2016; Aubrun 2008; Dahl 2000; Grady 2012; Hercock 1999; Lo 2008; Sen 2009; Yalcin 2012). Pain scores were 3 mm lower in VAS (95% CI -4.6 to -0.5), among those who received ketamine compared to controls (Analysis 8.3). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 24 hours after total abdominal hysterectomy

No data were available for analysis on pain intensity at 24 hours during movement after total abdominal hysterectomy.

Pain intensity at rest at 48 hours after total abdominal hysterectomy

No data were available for analysis on pain intensity at rest at 48 hours after total abdominal hysterectomy.

Pain intensity during movement at 48 hours after total abdominal hysterectomy

No data were available for analysis on pain intensity at 48 hours during movement after total abdominal hysterectomy.

Pain intensity at rest at 24 hours after laparoscopic procedures

Nine studies assessed ketamine's effect on pain intensity at rest at 24 hours after laparoscopic procedures (Ayoglu 2005; Karcioglu 2013; Kwok 2004; Leal 2013; Leal 2015; Lin 2016; Mathisen 1999; Nesek-Adam 2012; Papaziogas 2001). Pain scores were 2 mm lower (95% CI -6.7 to 2.0), in VAS among 267 participants who received ketamine compared to 217 participants who served as controls (Analysis 9.3). We assessed the quality of evidence for this outcome as low, downgraded once because there were fewer than 1500 participants in the analysis, and once because it was not possible to test for small-study effects.

Pain intensity during movement at 24 hours after laparoscopic procedures

No data were available for analysis on pain intensity at 24 hours during movement after laparoscopic procedures.

Pain intensity at rest at 48 hours after laparoscopic procedures

No data were available for analysis on pain intensity at rest at 48 hours after laparoscopic procedures.

Pain intensity during movement at 48 hours after laparoscopic procedures

No data were available for analysis on pain intensity at 48 hours during movement after laparoscopic procedures.

Appendix 6. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Higgins 2011).

- **High**: randomised trials; or double-upgraded observational studies
- **Moderate**: downgraded randomised trials; or upgraded observational studies
- **Low**: double-downgraded randomised trials; or observational studies
- **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias.

WHAT'S NEW

Date	Event	Description
21 January 2021	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 1, 2016
Review first published: Issue 12, 2018

Date	Event	Description
11 January 2019	Amended	Typo corrected in author SS's declaration of interest.
18 September 2017	Amended	See Published notes.
14 June 2017	Amended	This protocol has been withdrawn. See Published notes.

CONTRIBUTIONS OF AUTHORS

ECVB and VKK developed the search strategy, ECVB wrote and VKK revised the background section, ECVB and ET were responsible for the data extraction, and ECVB, ET and VKK were responsible for the data analysis; RAM completed sensitivity analyses. VKK and RAM acted as guarantors of the review. All review authors were responsible for completing the protocol and the review, and will be responsible for updating the review in future.

DECLARATIONS OF INTEREST

ECVB: none known. ECVB is a specialist physician in anaesthesiology and intensive care medicine and she treats patients suffering from acute postoperative pain.

ET: none known. ET is a specialist physician in anaesthesiology and intensive care medicine and she treats patients suffering from acute postoperative pain.

MH: none known. MH is a specialist physician in anaesthesiology and he treats patients with acute postoperative and chronic pain.

RFB: none known. RFB is a specialist pain physician (retired).

SS's institution (University of Alberta) received fees for his contribution to an advisory board from Daiichi Sankyo, Inc. (2015). SS is a specialist occupational medicine physician and some of the patients he assesses have painful conditions.

RAM has received grant support from Grünenthal relating to individual patient-level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015), and Novartis for a network meta-analysis on acute postoperative pain using data from Cochrane Reviews. He has received honoraria for attending boards with RB on understanding pharmacokinetics of drug uptake (2015). He has received honoraria from Omega Pharma (2016), and Futura Pharma (2016), for providing advice on trial and data analysis methods.

VK: none known. VK is a specialist physician in anaesthesiology and intensive care medicine and he treats patients suffering from acute postoperative pain.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- State funding for university-level health research (grant TYH2014305), Finland

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We realised that in the protocol we had inadvertently included postoperative hyperalgesia assessment as both a secondary outcome and (incorrectly) as a subgroup analysis.
- We have changed the method of testing for statistical heterogeneity to the I^2 statistic.
- We have assessed the possible bias in blinding as two separate domains: blinding of participants and personnel (performance bias), and blinding of outcome assessment (checking for possible detection bias). This is also presented as two separate domains in the 'Risk of bias' table. Additionally, we present an assessment concerning selective reporting (checking for reporting bias), and considered other possible biases.
- In the review, we have specified that the opioid consumption registered is milligrams of morphine equivalents. If the opioid administered for postoperative analgesia was other than morphine we converted it to morphine equivalents using equations found in the literature. Studies refer to postoperative analgesic use, but this was exclusively use of opioids.
- We changed the unit of analysis of this review from individual, participant-level data to study-level data because participant-level data were not available except for two studies (Joseph 2012; Lo 2008).
- If confidence intervals alone were presented, we derived standard deviations from confidence interval data (Higgins 2011a).
- We observed a wide heterogeneity considering surgery types between studies to be included in this analysis. From a clinical point of view and to better serve clinical decision making, in addition to analysing a non-stratified study population, we decided to analyse the main outcomes separately for different surgery types.
- One additional subgroup analysis related to the use of benzodiazepines as premedicant. The potential for interaction was highlighted in the protocol, but not mentioned as a subgroup analysis at that time.
- We added sections, 'Subgroup analysis and investigation of heterogeneity' and 'Sensitivity analyses' to the full review.

- We performed an additional sensitivity analysis on pain intensity with placebo, as many studies had pain scores indicating little or no pain, blunting the ability to detect an analgesic effect. Additionally, we performed sensitivity analysis according to study size (30 or more and 50 or more participants in treatment arms).
- We included assessment of the quality of evidence in this review. We did not use GRADEpro GDT 2015 to determine levels of evidence because it did not consider important issues such as small study size (which predominated in our included studies), and other factors that could have affected judgement about study quality. Because we observed a wide range of surgery types we decided to analyse the primary outcomes separately for different surgery types and present the analyses in appendices. This was to better serve clinical decision making, and to support GRADE decisions.
- We limited study size to a minimum of 10 participants completing the study in each trial arm, to be consistent with this practice in many pain and anaesthesia reviews, and because of the considerable concerns about small study size as a source of heterogeneity and bias. For these reasons we also performed a sensitivity analysis to check that the overall result was also reflected by the largest studies, least likely to suffer from problems of random chance or small study bias.
- We created a grid to help with consistent judgements about GRADE, relating to study size and presence or absence of small-study effects.
- Because reports did not categorise adverse events as major or minor, we pooled all adverse event reports together.

NOTES

Assessed for updating in 2021

In January 2021 we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be reassessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Analgesics [*administration & dosage] [adverse effects]; Analgesics, Opioid [administration & dosage]; Central Nervous System Diseases [chemically induced]; Hyperalgesia [epidemiology]; Injections, Intravenous; Ketamine [*administration & dosage] [adverse effects]; Morphine [administration & dosage]; Pain Measurement; Pain, Postoperative [*drug therapy]; Postoperative Nausea and Vomiting [epidemiology] [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans