Paper II

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Perioperative ketamine for acute postoperative pain (Review)

Bell RF, Dahl JB, Moore RA, Kalso E

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ABSTRACT

Background
Postoperative pain management is often limited by adverse effects such as nausea and vomiting. Adjuvant treatment with an inexpensive opioid-sparing drug such as ketamine may be of value in giving better analgesia with fewer adverse effects.

Objectives
To evaluate the effectiveness and tolerability of ketamine administered perioperatively in the treatment of acute postoperative pain in adults.

Search strategy
Studies were identified from MEDLINE (1966-2004), EMBASE (1980-2004), the Cochrane Library (2004) and by handsearching reference lists from review articles and trials. The manufacturer of ketamine (Pfizer) provided search results from their in-house database, PARDLARS.

Selection criteria
Randomised controlled trials (RCTs) of adult patients undergoing surgery, being treated with perioperative ketamine or placebo. Studies where ketamine was administered in addition to a basic analgesic (such as morphine or NSAID) in one study group, and compared with a group receiving the same basic analgesic (but without ketamine) in another group, were also included.

Data collection and analysis
Two independent reviewers identified fifty five RCTs for potential inclusion. Quality and validity assessment was performed by two independent reviewers. In the case of discrepancy, a third reviewer was consulted. Patient reported pain intensity and pain relief was assessed using visual analogue scales or verbal rating scales and adverse effects data were collated.

Main results
Thirty-seven trials were included (2240 participants). Eighteen trials were excluded. Twenty-seven of the 37 trials found that perioperative subanaesthetic doses of ketamine reduced rescue analgesic requirements or pain intensity, or both. Quantitative analysis showed that treatment with ketamine reduced 24 hour PCA morphine consumption and postoperative nausea or vomiting (PONV). Adverse effects were mild or absent.

Authors' conclusions
Ketamine in subanaesthetic dose (that is a dose which is below that required to produce anaesthesia) is effective in reducing morphine requirements in the first 24 hours after surgery. Ketamine also reduces postoperative nausea and vomiting. Adverse effects are mild or absent.

PLAIN LANGUAGE SUMMARY

Perioperative ketamine in subanaesthetic dose reduces postoperative morphine requirements and reduces postoperative nausea or vomiting (PONV).

Adverse effects for perioperative ketamine are mild or absent. The current data cannot be translated into a specific treatment regime.

BACKGROUND

Adverse effects such as nausea and vomiting often limit postoperative pain management. There are a number of reasons for postoperative nausea and vomiting (PONV), and these have been exhaustively discussed in the anaesthetic literature. One possible factor is the use of opioids and adjuvant treatment with opioid-sparing drugs such as ketamine may be of value in giving better analgesia with fewer adverse effects (Schmid 1999).

Ketamine is a phencyclidine derivative developed in the 1960's as a general anaesthetic. Ketamine hydrochloride is given intravenously or intramuscularly for surgical anaesthesia. Ketamine is also used as an adjuvant to opioids in the treatment of refractory pain in cancer patients (Bell 2003), in the treatment of neuropathic pain (Fisher 2000), and in the treatment of acute postoperative pain (Schmid 1999), although not licensed for these conditions. Ketamine for postoperative pain may be administered before incision, after incision, or in the postoperative period, and is usually given as an adjuvant to systemic opioid, for example patient-controlled analgesia (PCA). Routes of administration include intravenous, subcutaneous, epidural, transdermal and intra-articular. Ketamine was previously only available as a racemic mixture of two enantiomers, S(+) and R(-) ketamine. The S(+) isomer has been shown to be approximately twice as potent as the racemic mixture (Arendt-Nielsen 1996). S(+) ketamine has recently been approved for clinical use in countries such as Finland and Germany. Clinical use of ketamine is limited due to psychotomimetic adverse effects such as hallucinations and bad dreams. Other common adverse effects are dizziness, blurred vision, and nausea and vomiting.

Opioids are traditionally used as a part of general anaesthesia and for the treatment of acute postoperative pain. Recent research indicates that opioids produce not only analgesia, but also hyperalgesia (Mao 2002). Consequently, perioperative (pre, per, and postoperative) opioids may increase postoperative pain and opioid requirements (Guignard 2000). Central sensitization includes an altered processing of innocuous, tactile impulses from myelinated afferents so that activation of these fibres produces painful sensations (Woolf 2000). The neurophysiological and biochemical mechanisms of these alterations include a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, mediated by wind-up and neurokinin and N-methyl-D-aspartic acid receptor mechanisms (NMDA receptors) (Woolf 2000). Wind-up is a phenomenon whereby responses of dorsal horn neurones increase during repetitive, constant intensity, C-fiber 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 (Price 2000; Mao 2002). Ketamine is a non-competitive NMDA receptor antagonist. NMDA receptor blocking could be a fruitful therapy for improving postoperative opioid effectiveness. Ketamine could, in addition to having an opioid sparing effect, conceivably reduce the development of chronic postoperative pain through NMDA receptor blockade and reduction of wind-up and central sensitization.

Published literature indicates that ketamine is used in the perioperative setting in countries such as Greece, Brazil, India, Germany, UK, Israel, France, China, Denmark, Norway, and Japan for anaesthesia or as an adjuvant analgesic. However, current use of ketamine in this setting involves different practice regarding dose, route of administration and time of administration. A literature review based on an electronic search of the MEDLINE database from 1966-1998 (Schmid 1999) concludes that the role of ketamine remains controversial, but that low-dose ketamine (defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route) as an adjuvant to opioids or local anaesthetics may have an important role to play in the treatment of acute postoperative pain. This review will consider the evidence for the efficacy and tolerability of ketamine in the treatment of acute postoperative pain in adults.

OBJECTIVES

To evaluate the effectiveness and tolerability of ketamine administered perioperatively (pre, per, and postoperative) in the treatment or prevention of acute, postoperative pain in adults.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized, placebo-controlled trials described as double-blinded and where each group had a minimum of ten patients who had completed the study were included. Studies where ketamine was administered in addition to a basic analgesic (such as morphine or NSAID) in one study group, and compared with a group receiving the same basic analgesic (but without ketamine) in another group, were also included. All identified published trials were considered eligible. Only complete studies, not abstracts, were included. Duplicate publications are reported but excluded from the analysis.

Types of participants

The population addressed by the review were patients aged 18 years or above, undergoing a surgical procedure.

Types of intervention

The intervention considered by this review was treatment with ketamine, given systemically or spinally, in any dose during the perioperative period. Participants received ketamine or placebo, or both ketamine and basic analgesic or basic analgesic alone.

The ketamine or placebo or basic analgesic was administered:
A: As a bolus dose prior to incision (pre-incisional bolus)
B: As a bolus dose immediately after incision or at wound closure (post-incisional bolus)
C: An infusion (or repeated by-the-clock dosing) begun prior to incision
D: Same as C, but begun after incision
E: As a postoperative bolus or infusion, including PCA

Types of outcome measures

The primary outcome measure

- For studies using PCA (E above) was total consumption of opioids or other analgesics for up to 48 hours after surgery.
- For studies not assessing or using PCA, and in the absence of rescue medication, was pain intensity assessed using subjective, validated measures of pain on movement and at rest (e.g., visual analogue scale of pain intensity (VASpi) or other validated scales). If rescue medication was given, the consumption of rescue medication was used as the outcome (Kalso 2002).

Secondary outcome measures included:

- Time from end of surgery to first request for analgesia/first trigger of PCA.
- Major and minor adverse events as judged by the author of the study, such as hallucinations, bad dreams, dizziness, blurred vision, sedation, nausea, and vomiting.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Pain, Palliative and Supportive Care Group methods used in reviews.

ELECTRONIC DATABASES
To identify studies for inclusion in this review, detailed search strategies were developed for each electronic database searched. These searches were based on the search strategy developed for the Cochrane Central Register of Controlled Trials (CENTRAL) and revised appropriately for each database. The subject search used a combination of controlled vocabulary and free text terms as follows:

#1. KETAMINE single term (MeSH)
#2. ketamine OR ketalar
#3. (#1 or #2)
#4. PAIN POSTOPERATIVE single term (MeSH)
#5. (postoperat* near pain*)
#6. (pain* next following next surg*)
#7. (pain* next following next treat*)
#8. (pain* next following next operat*)
#9. post-operat* pain
#10. ((post near surg*) or postsurg* OR post-surg*)
#11. ((post near operat*) or postoperat* OR post-operat*)
#12. pain*
#13. #10 AND #11
#14. (#13 and #12)
#15. (post-operat* near analgesi*)
#16. (postoperat* near analgesi*)
#17. (post-surg* near analgesi*)
#18. (postsurg* near analgesi*)
#19. (analgesi* near (following next surg*))
#20. (analgesi* next following next operat*)
#21. (#4 or #5 or #6 or #7 or #8 or #9 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#22. (#3 and #21)

The search strategies for EMBASE and PARDLARS are given in Table 01.

The following electronic databases were searched:

1. Cochrane Pain, Palliative & Supportive Care Register (current issue)
2. The Cochrane Central Register of Controlled Trials (CENTRAL): The Cochrane Library (June 2004)
3. MEDLINE (1966 -June 2004)
4. EMBASE (1980 -June 2004)
5. PARDLARS (Pfizer Corporation's in-house database) February 2003

HANDSEARCHING
Journals were not hand searched. Abstracts were checked to see if they had been published. Reference lists were handsearched (see below).

REFERENCE LISTS
The reference lists of all eligible trials, key textbooks, and relevant systematic reviews were searched for additional studies.

UNPUBLISHED DATA
The manufacturers of ketamine (Ketalar), Pfizer plc, were contacted to request access to relevant research material and unpublished data.

LANGUAGE
There was no language restriction. The search attempted to identify all relevant studies irrespective of language. Non-English papers were assessed and, if necessary, translated with the assistance of a native speaker.

METHODS OF THE REVIEW

STUDY SELECTION

All identified records from each of the databases were examined. The titles and abstracts of studies were studied independently by two reviewers (RB, EK) and potentially relevant studies, including review articles, were retrieved for assessment for inclusion in the review. Each trial report which appeared to meet the criteria was independently assessed for inclusion by three reviewers (RB, JBD, EK).

DATA EXTRACTION

A data extraction form was designed and the following data items were collected:

1. Publication details
2. Patient population, number of patients, age, surgical procedure
3. Description of intervention
4. Design, study duration and follow up
5. Outcome measures
6. Analgesic outcome results
7. Withdrawals and adverse effects

STUDY QUALITY AND VALIDITY

Study quality (randomization/allocation concealment; details of blinding measures (Colditz 1989; Schulz 1995); withdrawals and dropouts; overall quality score) were evaluated using the three item (1-5) Oxford Quality scale (Jadad 1996).

Validity was evaluated using the 5 item (1-16) Oxford Pain Validity Scale (OPVS) (Smith 2000). Heterogeneity tests were not used as they have previously been shown to be unhelpful (Morris 1995; Gavaghan 2000) although clinical homogeneity was examined visually (Higgins 2002). Scoring was performed independently by two reviewers (RFB, EK). In the case of discrepancy, a third reviewer (JBD) was consulted.

ANALYSIS

Both dichotomous and continuous data were extracted. Meta-analysis was performed where appropriate. The data did not permit calculation of odds ratios, numbers needed to treat (NNTs) or numbers needed to harm (NNHs) with 95% confidence intervals. Continuous data were analysed as weighted mean differences (WMD).

Subgroup analysis was not possible due to the heterogeneity of the trials.

DESCRIPTION OF STUDIES

The searches identified a total of 165 possible titles. Seventy-three were excluded. Eighteen were not clinical trials. Thirty-eight were abstracts. Thirteen trials did not concern postoperative pain. One was a retrospective study. One paper (Gilabert Morell 2002) was irretrievable. Two were duplicates (Dick 1983, Knoche 1983). In addition, eight trials were not randomised and fifteen did not have an appropriate control. Fourteen trials were not described as double-blind. A total of 55 randomised, controlled, double-blind clinical trials of perioperative administration of ketamine for postoperative pain control were identified. Eighteen trials were excluded: five due to the adminstration form of ketamine) (two transdermal, two intra-articular, one wound instillation). Four trials were excluded because groups contained less than the minimum of ten patients who had completed the study. Nine trials were excluded due to methodological flaws. Details of these 18 trials may be seen in the table of excluded studies.

Thirty-seven trials with 53 treatment arms met the inclusion criteria (2240 participants). One study in Turkish (Talu 2002) was assessed with the help of a native speaker. Details of these trials may be seen in the table of included studies and in Additional Table 1.

These 37 trials with 53 treatment arms could be divided into:

A. 13 treatment arms with a preincisional IV or IM bolus of ketamine compared with placebo

B. 7 treatment arms with an IV-bolus of ketamine at wound closure compared with placebo

C. 13 treatment arms with a perioperative continuous infusion/ repeated boluses of IV-ketamine compared with placebo

D. 7 treatment arms with administration of a preincisional bolus of epidural ketamine

E. 3 treatment arms with administration of a postincisional bolus of epidural ketamine

F. 2 treatment arms with administration of a continuous perioperative epidural infusion of ketamine compared with placebo

G. 2 treatment arms with intraoperative IV ketamine versus placebo combined with postoperative PCA ketamine/morphine versus PCA morphine

H. 4 treatment arms with postoperative IV PCA ketamine/morphine, compared with IV PCA morphine

I. 2 treatment arms with patient-controlled epidural analgesia (PCEA) ketamine +morphine (and other drugs), compared with PCEA morphine (and other drugs)

Twenty-six trials had a placebo control while 11 trials with ketamine in addition to a basic regimen with morphine was compared with morphine alone. A total of 2137 patients, of which 1210 received ketamine, were studied. Pain was rated using visual analogue scale (VAS) in 34 trials, and a verbal rating scale (VRS) was used in three.

The most common route of administration of ketamine was intravenous, as a bolus or infusion, or both. In six trials ketamine was administered as an epidural bolus. PCA ketamine was used in four studies and PCEA ketamine in two. Thirty-two trials used racemic ketamine, four trials used S (+) ketamine and one trial used the R (-) isomer.

A. Studies with administration of a preincisional IV or IM bolus of ketamine compared with placebo

Twelve trials with 13 treatment arms compared a preincisional bolus dose of ketamine with placebo. R (-) ketamine was used in one treatment arm (Mathisen 1999), S(+) ketamine in one treatment arm (Argiriadou 2004) and racemic ketamine in 11 treatment arms.

The retrieved trials were heterogeneous. The doses of ketamine varied almost seven-fold, from 0.15 to 1.0 mg/kg IV. Different analgesics and treatment regimens were employed for rescue medication, and the surgical procedures included various gynaecological, abdominal, and orthopedic operations. Due to this disparity, a meta-analysis of the combined results was not considered rational. In one of these trials having two treatment arms, one pre and one postincisional, all patients had been pretreated with IM ketorolac together with preincisional skin infiltration with bupivacaine (Mathisen 1999). This trial was scored as non-sensitive.

B. Studies with administration of an IV-bolus of ketamine at wound closure compared with placebo

Five trials with seven treatment arms compared a postincisional bolus dose of ketamine with placebo. R (-) ketamine was used in one (Mathisen 1999), and racemic ketamine in six treatment arms.

Again the trials were heterogenous and involved such different surgical procedures as elective outpatient surgery and abdominal hysterectomy. Ketamine doses ranged from 0.05 to 1 mg/kg. Two studies (Menigaux 2000, Mathisen 1999) used PCA opioid for postoperative pain and three studies used incremental IV-opioid bolus on request.

C. Studies with administration of a perioperative continuous infusion/repeated boluses of IV-ketamine compared with placebo

Eleven trials with 13 treatment arms compared a perioperative continuous intravenous infusion/repeated IV bolus of ketamine with placebo. A ketamine infusion was used in 12 treatment arms, and repeated intraoperative bolus of ketamine at twenty minute intervals in one (Argiriadou 2004). S (+) ketamine was used in two treatment arms (Argiriadou 2004; Jaksch 2002) and racemic ketamine in 11.

The surgical procedures varied and included predominantly major abdominal and renal surgery. There was clinical heterogeneity, with wide variation in the total ketamine dose administered due to different doses and duration of infusions. In seven treatment arms, the infusion was commenced prior to incision and continued until skin closure. In one treatment arm, ketamine was commenced prior to incision and infused until a total dose of 2 mg/kg had been given (Kakinohana 2004). In five treatment arms, the infusion was commenced prior to incision and continued for 2-72 hours postoperatively. In two treatment arms, a ketamine infusion was commenced after surgery and continued in one arm for 24 hours (Adriaenssens 1999) and in the other for 48 hours (Guillou 2003). Different analgesics and treatment regimens were employed for rescue medication, one treatment arm (Adriaenssens 1999) investigated PCA IV ketamine. Eight arms used PCA morphine for postoperative pain (table 3) while two arms used patient controlled epidural analgesia (PCEA) morphine (Aida 2000 A,B) and two arms used PCEA morphine and bupivacaine (Kakinohana 2004, Kararmaz 2003).

In one arm, all patients received epidural bupivacaine 2.5 mg/ml, 4 ml/hr for 0-24 hours postoperatively (Ilkjær 1998). This was a trial with negative outcome and was considered potentially non-sensitive. However, since the patients experienced pain above 30 on the VAS during movement in the early postoperative period, and to avoid bias, the trial was included in the quantitative analysis.

D. Studies with administration of a preincisional bolus of epidural ketamine

Seven trials with seven treatment arms investigated a preincisional epidural bolus of ketamine. Two trials with two treatment arms investigated a preincisional epidural bolus of ketamine and morphine compared with morphine alone. Racemic ketamine was used in six treatment arms, while S(+) ketamine was used in one (Himmelseher 2001). These trials concerned major surgical procedures such as total abdominal hysterectomy, colectomy, gastrectomy and total knee arthroplasty. The ketamine doses varied from 0.25 mg/kg bolus to 1 mg/kg.

E.Studies with administration of a postincisional bolus of epidural ketamine

Three trials with three treatment arms investigated a postincisional epidural bolus of ketamine. Two trials investigated epidural ketamine + morphine, compared with epidural morphine alone (Santawat 2002, Subramaniam 2001(b)). One trial compared epidural ketamine with placebo (Abdel-Ghaffar 1998). All trials used racemic ketamine. Two trials used a ketamine dose of 30 mg while the third trial used a dose of 1 mg/kg.

F.Studies with administration of a continuous perioperative epidural infusion of ketamine compared with placebo

One trial with two treatment arms (De Kock 2001) investigated an epidural bolus of ketamine followed by an epidural infusion of ketamine until the end of surgery, compared to a control group (no ketamine). This trial used racemic ketamine at a dose of 0.25 mg/kg bolus + 0.125 mg/kg/h in one treatment arm and 0.5 mg/kg and 0.25 mg/kg/h in the other.

G. Studies with intraoperative IV ketamine versus placebo combined with postoperative PCA ketamine/morphine versus PCA morphine

Two trials with two treatment arms investigated intraoperative IV ketamine combined with postoperative PCA ketamine + morphine, compared to peroperative placebo and postoperative PCA morphine. One trial (Snijdelaar 2004) used a preincisional IV bolus of S (+) ketamine 0.1 mg/ kg followed by a continuous infusion of 0.002 mg/kg/min until skin closure and IV PCA ketamine + morphine, with bolus dose of 0.5 mg ketamine + 1 mg morphine. The second trial (Hercock 1999) used a single 0.3 mg/kg IV bolus of racemic ketamine after induction and postoperative IV PCA ketamine 1 mg/ml + morphine 1 mg/ml.

H.Studies with postoperative IV PCA ketamine/morphine, compared with IV PCA morphine

Four trials with four treatment arms investigated postoperative IV PCA ketamine + morphine, compared to IV PCA morphine. Racemic ketamine was used in all trials. Doses ranged from 0.75 to 2 mg/ml. The morphine dose was 1 mg/ml in three trials and 0.4 mg/ml in one trial. One trial was judged to be potentially non-sensitive since 60-70% of the patients were pain free for the first four hours after surgery (Murdoch 2002).

I.Studies with PCEA ketamine +morphine (and other drugs), compared with PCEA morphine (and other drugs)

Two trials with two treatment arms investigated PCEA ketamine + morphine , compared with PCEA morphine. These studies were performed in patients undergoing major thoracic or abdominal surgery. Racemic ketamine was used in both treatment arms. One treatment arm used a multimodal PCEA regime, with a basal infusion of ketamine 0.4 mg/ml + morphine 0.02 mg/ml, in addition to bupivacaine and epinephrine, and a bolus dose of 2.5 ml (Chia 1998). The other treatment arm used a loading dose of ketamine 5 mg + morphine 1 mg, followed by a basal infusion with ketamine 0.5 mg/ml + morphine 0.2 mg/ml, 1 ml/h and 1 ml bolus (Tan 1999).

METHODOLOGICAL QUALITY

The included studies were assessed by three independent reviewers using two quality measures: the Oxford scale (Jadad 1996) and the Oxford Pain Validity Scale (Smith 2000).

Quality and validity scores were generally high with a mean quality score of 3.9 and a mean validity score of 10.3. Three trials were considered non-sensitive (Ilkjær 1998, Mathisen 1999, Murdoch 2002).

RESULTS

A. Studies with administration of a preincisional IV or IM bolus of ketamine compared with placebo (13 treatment arms, N (ketamine treated) =266)

Postoperative analgesic requirements were reduced by preincisional ketamine bolus in eight out of 13 treatment arms. In one treatment arm postoperative morphine consumption was reduced by over 50% (Kwok 2004). In two treatment arms, postoperative morphine consumption was reduced by over 40% (Menigaux 2000; Roytblat 1993). In one treatment arm, the number of patients requiring morphine was reduced from 9/25 to 3/25 (Menigaux 2001). In two treatment arms the number of rescue doses of IM diclofenac was reduced from 4 to 2, and from 3 to 1.5, respectively (Lauretti 1996). In five treatment arms there was no significant difference in postoperative analgesic requirements between ketamine and placebo groups.

VAS pain scores were reduced for up to 24 hours postoperatively in seven of the 13 treatment arms.

B. Studies with administration of an IV-bolus of ketamine at wound closure compared with placebo (seven treatment arms, N (ketamine treated) =212)

In three of seven treatment arms, postoperative morphine requirements were reduced by postincisional ketamine. In one trial, morphine consumption was reduced by 50% (Menigaux 2000). In another trial with three treatment arms, ketamine doses of 75μg/kg and 100 μg/kg IV, given together with morphine 50 μg/kg IV reduced postoperative morphine requirements by approximately 40% (Suzuki 1999). A ketamine dose of 50μg/kg IV had less effect on both morphine consumption and pain scores.

VAS pain scores were reduced in four out of seven treatment arms: for up to 45 minutes postoperatively in three treatment arms and up to six hours postoperatively in one treatment arm. In three treatment arms there was no significant difference in VAS pain scores.

C. Studies with administration of a perioperative continuous infusion/ repeated boluses of IV-ketamine compared with placebo (13 treatment arms, N (ketamine treated) =290)

Ketamine treatment reduced postoperative analgesic requirements in 9 out of 13 treatment arms. In one treatment arm, morphine consumption was reduced by approximately 30% (Guignard 2002). In another trial with two ketamine treatment arms, the combination of peroperative epidural morphine and IV ketamine gave 100% reduction in postoperative morphine requirements, while IV ketamine gave approximately 14% reduction (Aida 2000). In one treatment arm, PCA morphine consumption was reduced approximately 30 % from 0-24 hours, while cumulative morphine requirements at 48 hours in the placebo group were almost twice that of the ketamine group (Adriaenssens 1999).

VAS pain scores were reduced in seven out of 13 treatment arms: at one hour in two arms, up to six hrs in two arms, and up to 48 hours postoperatively in another two treatment arms (Aida 2000). In one treatment arm, both VAS at rest and on movement were reduced at all time points (Kakinohana 2004). In one treatment arm VAS at rest was reduced from 0-6 hrs, while VAS on coughing was reduced at all timepoints (Kararmaz 2003). There was no difference detected in pain scores in 6 of 13 treatment arms.

D. Studies with administration of a preincisional bolus of epidural ketamine (seven treatment arms, N (ketamine treated) = 119)

Consumption of rescue analgesics was reduced in only two out of seven treatment arms. In one treatment arm, the consumption of PCEA bupivacaine and fentanyl was reduced approximately 50% 4-24 hours postoperatively (Abdel-Ghaffar 1998).

Pain scores were reduced in three out of seven treatment arms. One trial did not provide pain score data (Subramaniam 2001(a)).

E.Studies with administration of a postincisional bolus of epidural ketamine (three treatment arms, N (ketamine treated)=61)

Analgesic consumption was reduced in two out of three treatment arms. Two treatment arms found no difference in pain scores. The third trial (Subramaniam 2001(b)) did not provide pain score data.

F.Studies with administration of a continuous perioperative epidural infusion of ketamine compared with placebo (two treatment arms, N (ketamine treated)=40)

There was no significant difference in postoperative analgesic consumption or pain scores.

G. Studies with intraoperative IV ketamine versus placebo combined with postoperative PCA ketamine/morphine versus PCA morphine (two treatment arms, N(ketamine treated)=37

Cumulative morphine consumption and pain scores at rest were reduced in one treatment arm (Snijdelaar 2004). There was no difference in morphine consumption or pain scores in the other treatment arm.

H.Studies with postop IV PCA ketamine/morphine, compared with IV PCA morphine (four treatment arms, N (ketamine treated)=110

Morphine consumption was reduced in two out of four treatment arms. In one trial (Javery 1996), mean morphine consumption was reduced by 50%, from 51.1 mg to 25.82 mg.

Pain scores were reduced in three out of four treatment arms.

I.Studies with PCEA ketamine +morphine (and other drugs), compared with PCEA morphine (and other drugs) (2 treatment arms, N (ketamine treated) =75)

Analgesic consumption was reduced in both treatment arms. In one treatment arm, the mean 24 hour cumulative analgesic volume was reduced from 96.6 ml to 74 ml. In the other treatment arm, the 24 hour mean morphine consumption was reduced from 8.6 mg to 6.2 mg.

Pain scores were reduced in both treatment arms. VAS at rest and on coughing was reduced on Day one in one, and VAS at rest was reduced from 0-3 hours in the other.

In summary, the need for rescue medication was reduced in 29 out of 53 treatment arms, whereas VAS or VRS pain intensity scores were reduced in 27 out of 51 treatment arms, pain score data not being given in the two remaining arms. No study reported an increased need for rescue medication, or higher VAS scores in the ketamine group.

When individual trials, rather than treatment arms, were examined, 27 out of 37 trials found that perioperative ketamine reduced rescue analgesic requirements or pain intensity, or both.

Ketamine dose

All trials used ketamine in subanaesthetic dose. The question of optimal ketamine dose is not resolved by these heterogenous trials. Out of interest, we wanted to see whether there was a dose-dependent effect. Using an "average" weight of 70 kg, we roughly calculated the mean 24 hour dose of ketamine for each of the trials included in the 24 hr PCA morphine meta-analysis. The trials could be divided into 4 groups: one group with an estimated dose of approximately 10 mg, one group with estimated dose of about 30 mg, a third group with estimated dose of about 65 mg and a fourth group with estimated dose 250-270 mg. Interestingly there seemed to be no increased morphine-sparing effect on increasing the ketamine dose above an estimated dose of 30 mg/ 24 hours.

Adverse effects

Two trials (Aida 2000, Talu 2002) did not report on adverse effects. In general, the occurrence of adverse effects was similar in ketamine and placebo treated groups.

Psychotomimetic adverse effects

Twenty-one of 37 trials specifically stated that there were no psychotomimetic adverse effects such as hallucinations, bad dreams or dysphoria. Psychotomimetic adverse effects were reported in four trials (Burstal 2001, Ilkjær 1998, Javery 1996, Subramaniam 2001(b)). Ilkjær 1998 reported that two patients in the ketamine group, and one in the placebo group, experienced psychomimetic side effects. Burstal 2001 reported withdrawal of four patients in the ketamine group due to dysphoria. Subramaniam 2001(b) reported one patient developing hallucinations after preoperative administration of ketamine, but no psychotomimetic adverse effects in the postoperative period. Javery 1996 reported one patient in the ketamine group experiencing dysphoria, compared with three in the control group.

Nausea and vomiting

One trial reported significantly less nausea in the ketamine treated group compared to placebo (Adriaenssens 1999). One trial reported significantly less nausea in the ketamine + morphine treated group, compared with the morphine group (Javery 1996). One trial reported significantly less nausea, vomiting and use of antiemetics in the ketamine group on the first postoperative day (Stubhaug 1997).

Sedation

Four trials (Guignard 2002; Ilkjær 1998; Mathisen 1999; Subramaniam 2001(a)) reported increased sedation in the ketamine-treated groups: Ilkjær 1998 reported significantly higher sedation scores for 0-24 hours after surgery. Guignard 2002 reported higher sedation scores for the first 15 minutes after extubation. Mathisen 1999 found that the placebo-treated group opened their eyes significantly faster and were extubated earlier than the R(-) ketamine treated groups. Subramaniam 2001(a) reported high sedation scores in six patients in the ketamine group, compared to none in the control group, for the first two hours after surgery, but no difference thereafter.

Diplopia

Diplopia as an adverse effect of ketamine was reported in three trials (Adriaenssens 1999, Jaksch 2002, Kararmaz 2003). Adriaenssens 1999 reported that two out of 15 ketamine treated patients experienced diplopia, while Jaksch 2002 reported diplopia in one out of 15 patients in the ketamine group. Kararmaz 2003

reported diplopia in three ketamine-treated patients, compared with none in the control group.

Quantitative Data Synthesis
The data did not permit the calculation of odds ratios, numbers-needed-to-treat (NNTs) or numbers-needed-to-harm (NNHs).

Meta-analysis of studies employing postoperative PCA-morphine
Twelve trials (Adriaenssens 1999; De Kock 2001; Guignard 2002; Guillou 2003; Ilkjær 1998; Jaksch 2002; Javery 1996; Menigaux 2000; Murdoch 2002; Roytblat 1993; Snijdelaar 2004; Stubhaug 1997) provided data on 24 hour cumulative IV PCA morphine consumption. The authors of nine trials were contacted in order to get the data expressed as means +/- SD. Six authors kindly provided the necessary data. Though the author of one trial (Roytblat 1993) could not be contacted, the data could be extracted from a figure. In two trials (De Kock 2001, Murdoch 2002) it was not possible to obtain the requested data.

In a total of 10 trials with 11 treatment arms and a total of 432 patients, treatment with ketamine significantly reduced PCA morphine consumption in the first 24 hours after surgery (WMD -15.98 mg with 95% CI (-19.70,-12.26)).

Meta-analysis of adverse effects with ketamine
Twenty-six out of 37 trials provided dichotomous data on nausea and vomiting, or nausea or vomiting. The total number of patients in the comparison was 1261. When all data was combined, treatment with ketamine significantly reduced postoperative nausea and vomiting (p=0.001). When the data for nausea and for vomiting alone were analysed, treatment with ketamine reduced nausea (p=0.03) and vomiting (p=0.002). When the data from trials included in the 24 hour PCA morphine consumption analysis was examined separately, ketamine reduced nausea and vomiting (p=0.03).

DISCUSSION

The objective of this systematic review was to assess the effectiveness and adverse effects of perioperative ketamine in the treatment of acute postoperative pain. Twenty-seven of 37 trials found that perioperative ketamine reduced rescue analgesic requirements or pain intensity, or both. Ten trials found no significant difference between ketamine and placebo, three of which were considered non-sensitive.

During the preparation of this review, two systematic reviews investigating ketamine for postoperative pain were published (Subramaniam 2004, Elia 2005). The authors of the first review (Subramaniam 2004) included 37 trials, including studies performed in children and also some trials excluded by our review. The primary outcome considered by the Subramaniam review was VAS scores in the first 24 hours after surgery. Due to the heterogeneity of the data, we have chosen to restrict quantitative analysis to 24 hour PCA morphine consumption and data on PONV. PCA morphine requirement is not the same as postoperative analgesic efficacy and not directly translatable to effect on postoperative pain, however use of rescue medication and pain intensity scores are common outcome measures in studies of postoperative pain.
The second review (Elia 2005) has similar findings to our own, with ketamine giving a clear decrease in 24 hour cumulative morphine consumption with a weighted mean difference of -15.7 mg. In contrast to our review, the authors found no decrease in PONV. This review included studies performed in children and in adults.

Ten trials with 11 treatment arms and 417 patients in the comparison, provided extractable data on 24 hour PCA morphine consumption. When this data was combined, ketamine was shown to be effective in reducing postoperative morphine requirements. This should be interpreted with caution since the number of patients is small, and doses and time of administration differ widely between trials. Performing separate meta-analysis on data from the separate treatment arms was considered but decided against, since the data were heterogenous and the number of patients in each analysis would be very small. The meta-analysis gave a weighted mean difference (WMD) of 15.98 mg. The clinical relevance of this dose reduction in the first 24 hours after surgery may be debated. When individual trial data were examined, including trials that were not included in the quantitative analysis, ketamine was generally reported to give a 30-50% reduction of rescue analgesics. A reduction of this order may well be clinically significant, especially in selected patient groups. Perioperative ketamine may be useful for patients who traditionally require larger doses of opioids, such as cancer patients on long-term opioid therapy or the drug-dependent patient population. Patients who are especially sensitive to the adverse effects of opioids, such as the elderly, may also be a target group for this treatment. Randomised, placebo controlled trials in these patient groups would be clinically relevant.

Elia *et al*. found that ketamine treatment did not reduce morphine-related adverse effects. They also found that the highest risk of hallucinations was in awake or sedated patients receiving ketamine without benzodiazepine, and that in patients undergoing general anaesthesia, the risk of hallucinations was low and independent of benzodiazepine premedication. In this review where surgery was performed under general anaesthesia in 35 of the 37 included trials, ketamine-related adverse effects were mild or absent. Elia *et al.* analysing data from 391 patients treated with ketamine and 284 patients receiving control, found no decrease in PONV. In contrast, our analysis of data from 705 patients treated with ketamine and 578 patients receiving control, showed a significant reduction of nausea and vomiting in ketamine-treated patients.

Issues of optimal dose and form of administration are not resolved by these trials. The most common route of administration for ketamine was intravenous bolus or infusion, or both, while 10 studies investigated epidural ketamine. Spinal ketamine is not a recommended route of administration due to unclear toxicity issues

(Schmid 1999). Whether the isomers S(+) or R(-) ketamine have advantages over the racemate is not clear from the current data.

Three studies (Illkjær 1998; Mathisen 1999; Murdoch 2002) were considered to be non-sensitive. The issue of study sensitivity in trial design is important. In general, sensitivity measures cannot be used for studies with PCA analgesic consumption as an endpoint (Kalso 2002). However, there are a number of factors which may decrease study sensitivity and which should be considered when designing clinical trials on postoperative pain. In one trial, all patients received a constant infusion of bupivacaine postoperatively (Illkjær 1998) while in another, all patients received pretreatment with ketorolac and preincisional skin infiltration with bupivacaine (Mathisen 1999). These factors may have been responsible for low levels of pain. These studies could produce false negative results as they would be unable to detect a difference between ketamine and placebo had there been one.

Only one study (De Kock 2001) included long-term follow-up regarding mechanical hyperalgesia and residual pain. An important question which has not been addressed in the current literature is whether ketamine prevents the development of hyperalgesia during surgery and/ or the development of chronic postsurgical pain. NMDA receptor antagonists, including ketamine, have been shown to prevent the development of hyperalgesia (Eide 1994, Angst 2003). Chronic postsurgical pain is more common than previously thought (Kalso 1992; Perttunen 1999; Nikolajsen 2004; Perkins 2000). Certain types of surgical intervention, for example thoracotomy and mastectomy, have a relatively high prevalence of chronic postsurgical pain. Studies with long term follow-up in these patient groups would therefore be of interest.

Ketamine is a readily available, inexpensive drug. It is generally thought that it has limited usefulness in pain management due to adverse effects. This is not supported by the current evidence in relation to acute postoperative pain in adults where adverse effects were mild or absent. In fact, ketamine reduces postoperative nausea and vomiting. Because both ketamine and morphine are reported to cause nausea and vomiting, it is interesting that a combination of morphine and ketamine appears to reduce PONV. When low-dose ketamine is given to healthy volunteers, the incidence of nausea and vomiting appears to be greater than that reported in the clinical setting (Schmid 1999). The observed reduction in PONV in the studies included in this review may be due to a morphine-sparing effect or to other as yet undetermined factors. Not all trials provided extractable data regarding nausea and vomiting. It is recommended that future trials report adverse effects as dichotomous data.

The large number of papers retrieved shows that there is considerable interest in the use of ketamine for acute postoperative pain. A number of studies are only published as abstracts. It will be interesting to see whether they are ultimately published, and how the new data will contribute to current findings.

AUTHORS' CONCLUSIONS

Implications for practice

Ketamine in subanaesthetic dose is effective in reducing morphine requirements in the first 24 hours after surgery. Adverse effects are mild or absent. Ketamine reduces postoperative nausea and vomiting.
The retrieved studies were heterogenous and the result of the meta-analysis can not be translated into any specific administration-regimen with ketamine.

Implications for research

Future trials should focus on optimal dose, dosing time and dosing periods, and have long-term follow-up with regard to the development of hyperalgesia and chronic postsurgical pain. Trials of perioperative ketamine in selected patient groups where opioid-sparing is desirable would be of interest. Better reporting of adverse effects, for example as dichotomous data, is required.

POTENTIAL CONFLICT OF INTEREST

RFB, JBD, RAM and EK have consulted for various pharmaceutical companies. RFB, JBD, RAM and EK have received lecture fees from pharmaceutical companies related to analgesics. No author has any direct stock holding in any pharmaceutical company.

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TABLES

Characteristics of included studies

Study	**Abdel-Ghaffar 1998**
Methods	Randomised, double-blind, placebo control
Participants	N= 61 Abdominal hysterectomy
Interventions	1. Ketamine 30 mg ED bolus before incision 2. Ketamine 30 mg ED bolus after incision
Outcomes	Pain intensity (VAS). Cumulative PCA consumption of ED fentanyl/ bupivacaine Time to first request for analgesia
Notes	Quality score:5 OPVS:13
Allocation concealment	A

Study	**Adriaenssens 1999**
Methods	Randomised, double-blind, placebo control
Participants	N= 30 Laparotomy
Interventions	Ketamine IV infusion, initially 10 mcg/kg/min for 48 hours after surgery
Outcomes	Pain intensity (VAS) PCA morphine consumption Adverse effects

Characteristics of included studies0 (*Continued*)

Notes	Quality score:2 OPVS: 6
Allocation concealment	A

Study	**Aida 2000**
Methods	Randomised, double-blind, placebo control
Participants	N=121 Distal or total gastrectomy
Interventions	1. Ketamine 1 mg/kg IV before surgical incision/ 0.5 mg/kg/h IV until skin closure 2. Morphine ED bolus prior to incision + infusion +placebo iv bolus + continuous infusion until skin closure 2. Placebo ED + ketamine iv bolus 1 mg/kg + infusion 0.5 mg/kg/hr 3. Morphine ED +ketamine iv
Outcomes	Pain intensity (VAS). Maximum 48 hr pain (categorical scale) PCA morphine consumption
Notes	Quality score:3 OPVS:8
Allocation concealment	A

Study	**Argiriadou 2004**
Methods	Randomised, double-blind, placebo control
Participants	N= 45 Major abdominal
Interventions	1.S(+) ketamine 0.5 mg/kg IV before surgical incision 2.Preincisional 0.5 mg bolus IV S(+) ketamine + intra- operative 0.2 mg/kg IV at 20 min intervals until end of surgery
Outcomes	Pain intensity (VAS) Cumulative consumption of diclofenac and dextropropoxyphene
Notes	Quality score:4 OPVS:9
Allocation concealment	A

Study	**Burstal 2001**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 70 Total abdominal hysterectomy
Interventions	Postop. PCA ketamine 2 mg/bolus IV
Outcomes	Pain intensity (VAS). Area of allodynia (Von Frey). PCA morphine consumption
Notes	Quality score: 5 OPVS: 14
Allocation concealment	A

Study	**Chia 1998**
Methods	Randomised, double-blind. Ketamine + morphine (+ other drugs) vs morphine (+ other drugs)
Participants	N= 91 Major intrathoracic or upper abdominal
Interventions	PCEA ketamine Basal infusion: 1 mg/ h, titrated.

Characteristics of included studies0 (*Continued*)

	Bolus:1 mg
Outcomes	Pain intensity (VAS) Cumulative total analgesic consumption
Notes	Quality score:4 OPVS: 12
Allocation concealment	A

Study	**Dahl 2000**
Methods	Randomised, double-blind, placebo control
Participants	N= 89 Abdominal hysterectomy
Interventions	1. Ketamine bolus 0.4 mg/kg IV prior to incision 2. Ketamine bolus 0.4 mg/kg IV at skin closure
Outcomes	Pain intensity (VAS, VRS). Rescue medication. Sleep. Level of activity. Adverse effects
Notes	Quality score:4 OPVS:13
Allocation concealment	A

Study	**De Kock 2001**
Methods	Randomised, double-blind, placebo control
Participants	N= 100 Rectal adenocarcinoma surgery
Interventions	1.±30 min before skin incision: ketamine bolus 0.25 mg/kg IV + infusion 0.125 mg/kg/hr IV until end of surgery 2. ±30 min before skin incision: ketamine bolus 0.5 mg/kg IV + infusion 0.25 mg/kg/hr IV until end of surgery. 3. 0.25 mg/kg ED bolus + 0.125 mg/kg/h ED until end of surgery. 4.0.5 mg/kg ED bolus + 0.25 mg/kg/h ED until end of surgery
Outcomes	Pain intensity (VAS). Area of hyperalgesia. Postoperative residual pain at 2 weeks, 1 month, 6 months, 1 year. Cumulative number of met and unmet PCA morphine demands
Notes	Quality score: 5 OPVS: 14
Allocation concealment	A

Study	**Guignard 2002**
Methods	Randomised, double-blind, placebo control
Participants	N= 50 Abdominal surgery
Interventions	Ketamine bolus 0.15 mg/kg IV +infusion 2 mcg/kg/min IV from prior to incision until skin closure
Outcomes	Pain intensity (VAS / 4 point VRS) Total morphine consumption (PCA and nurse-administered). Time to first request for morphine. Adverse effects
Notes	Quality score: 3 OPVS:9
Allocation concealment	A

Characteristics of included studies0 (*Continued*)

Study	**Guillou 2003**
Methods	Randomised, double-blind, placebo control
Participants	N= 101 Major abdominal
Interventions	After surgery: initial ketamine bolus 0.5 mg/kg IV + infusion 2mg/kg /min IV for 24 hr and 1mg/kg/min IV from 24-48 h
Outcomes	Pain intensity (VAS) Cumulative dose of PCA morphine
Notes	Quality score:4 OPVS:12
Allocation concealment	A

Study	**Hercock 1999**
Methods	Randomised, double-blind. Intraoperative IV ketamine vs placebo/ postoperative ketamine+morphine vs morphine
Participants	N= 50 Total abdominal hysterectomy
Interventions	After induction: ketamine bolus. 0.3 mg/kg IV. Postoperative IV PCA. 1 mg/bolus
Outcomes	Pain intensity (VRS). PCA morphine consumption
Notes	Quality score:4 OPVS:10
Allocation concealment	A

Study	**Himmelseher 2001**
Methods	Randomised, double-blind, placebo control
Participants	N= 42 Elective unilateral total knee arthroplasty
Interventions	S(+) ketamine bolus 0.25 mg/kg ED before surgical incision
Outcomes	Pain intensity (VAS). PCEA consumption of bupivacaine. Time to first request for analgesia. Adverse effects
Notes	Quality score:5 OPVS:11
Allocation concealment	A

Study	**Ilkjær 1998**
Methods	Randomised, double-blind, placebo control
Participants	N= 60 Elective nephrectomy or operation on pelvic structures
Interventions	Ketamine bolus 10 mg IV before surgical incision/10 mg/h IV postoperative infusion
Outcomes	Pain intensity (VAS). Nr. of PCA morphine doses. Pressure pain detection threshold. Pain sensitivity. Adverse effects
Notes	Quality score:4 OPVS:11
Allocation concealment	A

Characteristics of included studies0 (*Continued*)

Study	**Jaksch 2002**
Methods	Randomised, double-blind, placebo control
Participants	N=30 Elective arthroscopic anterior cruciate ligament repair
Interventions	S(+) ketamine bolus 0.5 mg/kg IV + infusion 2mcg/kg/hr IV until 2 hours after emergence from anaesthesia
Outcomes	Pain intensity (VAS). Time to first request for analgesia. PCA morphine consumption
Notes	Quality score:4 OPVS:13
Allocation concealment	A

Study	**Javery 1996**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 42 Lumbar microdiscectomy
Interventions	Postoperative IV PCA ketamine 1 mg/bolus
Outcomes	Pain intensity (VAS). PCA morphine consumption
Notes	Quality score:2 OPVS:9
Allocation concealment	A

Study	**Kakinohana 2004**
Methods	Randomised, double-blind, placebo control
Participants	N= 50 Elective open cholecystectomy
Interventions	Preincisional ketamine bolus 1 mg/ kg IV +1mgkg/hr IV infusion, maintained until 2 mg/kg given
Outcomes	Pain intensity (VAS) PCEA volume consumed
Notes	Quality score:3 OPVS:11
Allocation concealment	A

Study	**Kararmaz 2003**
Methods	Randomised, double-blind, placebo control
Participants	N= 40 Elective renal surgery
Interventions	Ketamine bolus 0.5 mg/kg IV + 0.5 mg/kg/h IV infusion until skin closure
Outcomes	Pain intensity (VAS) Mean PCEA analgesic consumption
Notes	Quality score:5 OPVS:13
Allocation concealment	A

Study	**Kirdemir 2000**
Methods	Randomised, double-blind, placebo control

Characteristics of included studies0 (*Continued*)

Participants	N= 30 Major abdominal surgery
Interventions	1. Preincisional bolus of ketamine 50 mg ED 2. Neostigmine ED
Outcomes	Pain intensity (VAS). Analgesic demand.
Notes	Quality score:3 OPVS:7
Allocation concealment	A

Study	**Kwok 2004**
Methods	Randomised, double-blind, placebo control
Participants	N= 135 Laparoscopic gynecological
Interventions	1.Preincisional bolus of ketamine 0.15 mg/kg IV 2. At wound closure: ketamine bolus 0.15 mg/kg IV
Outcomes	Pain intensity (VAS) Analgesic consumption
Notes	Quality score:5 OPVS:16
Allocation concealment	A

Study	**Lauretti 1996**
Methods	Randomised, double-blind, placebo control
Participants	N= 60 Anterior and posterior vaginoplasty
Interventions	1. Preincisional ketamine bolus 0.2 mg/kg IV + saline IT 2. Preincisional ketamine bolus 0.2 mg/kg IV + neostigmine IT 3. Fentanyl IV + neostigmine IT
Outcomes	Pain intensity (VAS). Time to first request for analgesia. Rescue medication. Adverse effects
Notes	Quality score:2 OPVS:8
Allocation concealment	A

Study	**Lehmann 2001**
Methods	Randomised, double-blind, placebo control
Participants	N= 80 Elective laparoscopic or proctologic surgery
Interventions	Preincisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS, VRS). Rescue medication. Adverse effects
Notes	Quality score:4 OPVS:12
Allocation concealment	A

Study	**Mathisen 1999**
Methods	Randomised, double-blind, placebo control

Characteristics of included studies0 (*Continued*)

Participants	N=60 Elective laparoscopic cholecystectomy
Interventions	1. Preincisional 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) PCA opioid consumption. Analgesics after discharge. Adverse effects
Notes	Quality score:5 OPVS:11
Allocation concealment	A

Study	**Menigaux 2000**
Methods	Randomised, double-blind, placebo control
Participants	N= 45 Knee surgery: elective arthroscopic anterior ligament repair
Interventions	1. Preincisional ketamine bolus 0.15 mg/kg IV 2. At wound closure: ketamine bolus 0.15 mg/kg IV
Outcomes	Pain intensity (VAS,VRS). PCA morphine consumption. Time to first request for analgesia. Degree of knee flexion. Adverse effects
Notes	Quality score:5 OPVS:12
Allocation concealment	A

Study	**Menigaux 2001**
Methods	Randomised, double-blind, placebo control
Participants	N= 50 Outpatient knee arthroscopy
Interventions	Preincisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS,VRS). Rescue medication. Adverse effects
Notes	Quality score:5 OPVS:14
Allocation concealment	A

Study	**Murdoch 2002**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 42 Total abdominal hysterectomy
Interventions	Postop. IV PCA ketamine 0.75 mg/bolus + morphine
Outcomes	Pain intensity (VRS) PCA morphine consumption
Notes	Quality score:4 OPVS:12
Allocation concealment	A

Study	**Papaziogas 2001**
Methods	Randomised, double-blind, placebo control

Characteristics of included studies0 (*Continued*)

Participants	N= 55 Elective laparoscopic cholecystectomy
Interventions	Preincisional bolus of ketamine 1 mg/kg IV
Outcomes	Pain intensity (VAS, VRS). Rescue medication. Time to first request for analgesia. Adverse effects
Notes	Quality score:3 OPVS:9
Allocation concealment	A

Study	**Roytblat 1993**
Methods	Randomised, double-blind, placebo control
Participants	N= 22 Elective open cholecystectomy
Interventions	Preincisional bolus of ketamine 0.15 mg/kg IV
Outcomes	Pain intensity (VAS,VRS). PCA morphine consumption. Time to first request for analgesia. Adverse effects
Notes	Quality score:3 OPVS:11
Allocation concealment	A

Study	**Santawat 2002**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 80 Gynaecological surgery
Interventions	1.Preincisional ED bolus of ketamine 30 mg + morphine 2. Postincisional ED bolus of ketamine 30 mg +morphine
Outcomes	Pain intensity VAS Analgesic consumption
Notes	Quality score:4 OPVS:11
Allocation concealment	D

Study	**Snijdelaar 2004**
Methods	Randomised, double-blind. Intraop. ketamine vs placebo / postop. ketamine + morphine vs morphine morphine and placebo controls
Participants	N= 28 Radical retropubic prostatectomy
Interventions	Intraoperative S (+) ketamine bolus 0.1 mg/kg IV, followed by continuous infusion of 0.002 mg/kg/min IV until skin closure+ postoperative IV PCA S (+) ketamine 0.5 mg bolus
Outcomes	Pain intensity (VAS) PCA morphine consumption
Notes	Quality score:5 OPVS:11
Allocation concealment	D

Study	**Stubhaug 1997**
Methods	Randomised, double-blind, placebo control

Characteristics of included studies0 (*Continued*)

Participants	N= 20 Nephrectomy (live kidney donors)
Interventions	Ketamine bolus 0.5 mg/kg IV + infusion 2 mcg/kg/min IV
Outcomes	Pain intensity (VAS). PCA morphine consumption. Area of punctate hyperalgesia. Pressure pain threshold. Adverse effects
Notes	Quality score:5 OPVS:12
Allocation concealment	A

Study	**Subramaniam 2001(a)**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 50 Major upper abdominal
Interventions	Preincisional bolus ketamine 1 mg/kg ED + morphine
Outcomes	Pain intensity (VAS) Nr. of doses ED morphine
Notes	Quality score:3 OPVS:10
Allocation concealment	A

Study	**Subramaniam 2001(b)**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 46 Major upper abdominal
Interventions	Postincisional ED bolus of ketamine 1 mg/kg +morphine
Outcomes	Pain intensity (VAS) Nr. of doses ED morphine
Notes	Quality score:4 OPVS:10
Allocation concealment	D

Study	**Suzuki 1999**
Methods	Randomised, double-blind, placebo control
Participants	N=140 Elective outpatient surgery (inguinal hernia repair, excision of skin lesions, breast or lymph node bipsy etc)
Interventions	IV- bolus of ketamine at wound closure: 1. 50 mcg/kg 2. 75 mcg/kg 3. 100 mcg/kg
Outcomes	Pain intensity (VAS) Rescue medication. Adverse effects
Notes	Quality score:5 OPVS:15
Allocation concealment	A

Study	**Talu 2002**
Methods	Randomised, double-blind, placebo control
Participants	N= 30

Characteristics of included studies0 (*Continued*)

	Thoracotomy
Interventions	1. Preincisional bolus of ketamine 1 mg/kg IM 2. Preincisional bolus of ketamine 0,5 mg/kg ED
Outcomes	Pain intensity (VAS) Postop. PCEA opioid and local anaesthetic consumption
Notes	Quality score:3 OPVS:10
Allocation concealment	A

Study	**Tan 1999**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 60 Lower abdominal
Interventions	PCEA ketamine Loading dose: 5 mg Basal infusion: 0.5 mg/h Bolus: 0.5 mg + morphine
Outcomes	Pain intensity (VAS) Morphine consumption
Notes	Quality score:2 OPVS:8
Allocation concealment	A

Study	**Xie 2003**
Methods	Randomised, double-blind, placebo control
Participants	N= 45 Selective gastrectomy
Interventions	1.Preincisional bolus of ketamine 0.5 mg/kg IV 2. Preincisional bolus of ketamine 0.5 mg/kg ED
Outcomes	Pain intensity (VAS) Morphine consumption
Notes	Quality score:4 OPVS:9
Allocation concealment	A

Study	**Ünlügenc 2003**
Methods	Randomised, double-blind. Ketamine + morphine vs morphine
Participants	N= 90 Major abdominal surgery
Interventions	1. Postop IV PCA ketamine 0.0125 mg/kg/bolus + morphine 2. Postop IV PCA morphine + magnesium
Outcomes	VRS PCA morphine consumption
Notes	Quality score:3

Characteristics of included studies0 (*Continued*)

	OPVS:12
Allocation concealment	A

ED= epidural
PCA= Patient controlled analgesia
IV = intravenous
IT = intrathecal
IM = intramuscular
OPVS= Oxford Pain Validity Scale
VAS= visual analogue scale
VRS=verbal rating scale
PCEA = Patient controlled epidural analgesia
mcg =microgram

Characteristics of excluded studies

Azevedo 2000	Transdermal ketamine
Clausen 1975	Inappropriate pain scale
Edwards 1993	Group size. Number of patients in group who completed the study less than 10
Heinke 1999	Methodological flaw. The primary outcome is PCA consumption of piritramide, but fixed maximum dose of piritramide
Huang 2000	Intra-articular ketamine
Joachimsson 1986	Inappropriate pain scale. Patients on ventilator
Kawana 1987	Group size. Number of patients in group who completed the study less than 10
Lauretti 2001	Transdermal ketamine
Reeves 2001	Different PCA settings
Sadove 1971	Inappropriate pain scale
Taura 2003	Unclear blinding. Different doses of morphine
Tok 1995	Intra-articular ketamine
Tverskoy 1994	Group size. Nr. of patients in group who completed the study less than 10
Tverskoy 1996	Group size. Nr. of patients in group who completed the study less than 10
Weinbroum 2003	Flawed randomization: "randomly enrolled into one of the two treatment protocols on alternate days"
Wong 1996	All patients pre-treated with ketamine
Zohar 2002	Wound instillation with ketamine
Ünlügenc 2002	Different PCA settings

ADDITIONAL TABLES

Table 01. Electronic search strategies

EMBASE	**PARDLARS**
#1 (NMDA) in TI (5188 records)	Product name contains KETAMINE
#2 N-methyl-D-aspartate (9584 records)	Full text: (POSTOPERATIVE OR POST-OPERATIVE) AND PAIN*

Table 01. Electronic search strategies (*Continued*)

EMBASE	PARDLARS
#3 #1 or #2 (12617 records)	
#4 ketamine or ketalar (20521 records)	
#5 postoperative near pain (11118 records)	
#6 post-operative near pain (713 records)	
#7 #5 or #6	
#8 random* (216674 records)	
#9 #3 or #4 (32042 records)	
#10 #9 and #7 (515 records)	
#11 #8 and #10 (167 records)	

ANALYSES

Comparison 01. Perioperative ketamine versus control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Morphine (PCA) consumption over 24 hours	9	372	Weighted Mean Difference (Fixed) 95% CI	-14.96 [-18.93, -9.00]

Comparison 02. Adverse effects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Nausea and vomiting			Relative Risk (Fixed) 95% CI	Subtotals only

COVER SHEET

Title	Perioperative ketamine for acute postoperative pain
Authors	Bell RF, Dahl JB, Moore RA, Kalso E
Contribution of author(s)	RFB was involved with searching, data extraction, quality scoring, analysis and writing. RFB and EK independently selected trials for inclusion in the review. EK was involved in analysis, quality and validity scoring and writing. JBD was involved with data extraction, analysis, quality and validity scoring and writing. RAM advised upon analysis and synthesis of quantitative data. All authors read and approved the final manuscript.
Issue protocol first published	2004/1
Review first published	2006/1
Date of most recent amendment	16 November 2005
Date of most recent SUBSTANTIVE amendment	17 October 2005
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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Editorial group	Cochrane Pain, Palliative and Supportive Care Group
Editorial group code	HM-SYMPT

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Perioperative ketamine versus control, Outcome 01 Morphine (PCA) consumption over 24 hours

Review: Perioperative ketamine for acute postoperative pain

Comparison: 01 Perioperative ketamine versus control

Outcome: 01 Morphine (PCA) consumption over 24 hours

Study	Ketamine N	Ketamine Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Adriaenssens 1999	15	19.40 (10.70)	15	30.70 (15.90)		16.7	-11.30 [-21.00, -1.60]
Guignard 2002	25	42.70 (16.30)	25	64.90 (27.00)		10.3	-22.20 [-34.56, -9.84]
Guillou 2003	41	37.00 (24.00)	52	48.00 (22.00)		17.5	-11.00 [-20.47, -1.53]
Ilkjær 1998	30	28.00 (21.00)	30	36.00 (23.00)		12.6	-8.00 [-19.14, 3.14]
Jaksch 2002	15	44.10 (45.23)	15	40.23 (17.16)		2.6	3.87 [-20.61, 28.35]
Javery 1996	22	25.82 (16.40)	20	51.10 (20.80)		12.1	-25.28 [-36.68, -13.88]
Roytblat 1993	11	29.50 (7.50)	11	48.70 (13.00)		20.0	-19.20 [-28.07, -10.33]
Snijdelaar 2004	13	32.15 (18.59)	12	50.42 (24.70)		5.3	-18.27 [-35.52, -1.02]
Stubhaug 1997	10	64.50 (22.60)	10	68.00 (30.00)		2.9	-3.50 [-26.78, 19.78]

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Study	Ketamine N	Ketamine Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	182		190			100.0	-14.96 [-18.93, -11.00]
Test for heterogeneity chi-square=11.40 df=8 p=0.18 I^2 =29.8%							
Test for overall effect z=7.40 p<0.00001							

-100.0 -50.0 0 50.0 100.0

Favours treatment Favours control

Analysis 02.01. Comparison 02 Adverse effects, Outcome 01 Nausea and vomiting

Review: Perioperative ketamine for acute postoperative pain

Comparison: 02 Adverse effects

Outcome: 01 Nausea and vomiting

Study	Ketamine n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Number of patients with nausea					
Abdel-Ghaffar 1998	17/41	11/20		14.0	0.75 [0.44, 1.29]
Adriaenssens 1999	1/15	6/15		5.7	0.17 [0.02, 1.22]
Guillou 2003	2/41	4/52		3.3	0.63 [0.12, 3.29]
Himmelseher 2001	2/18	5/19		4.6	0.42 [0.09, 1.91]
Jaksch 2002	7/15	4/15		3.8	1.75 [0.64, 4.75]
Karamaz 2003	1/20	6/20		5.7	0.17 [0.02, 1.26]
Kirdemir 2000	0/10	1/10		1.4	0.33 [0.02, 7.32]
Roytblat 1993	2/11	2/11		1.9	1.00 [0.17, 5.89]
Santawat 2002	34/40	31/40		29.4	1.10 [0.89, 1.36]
Subramaniam 2001(a)	11/26	11/24		10.9	0.92 [0.49, 1.72]
Tan 1999	8/30	11/30		10.4	0.73 [0.34, 1.55]
Ünlügenc 2003	5/30	9/28		8.8	0.52 [0.20, 1.36]
Subtotal (95% CI)	297	284		100.0	0.80 [0.65, 0.98]
Total events: 90 (Ketamine), 101 (Control)					
Test for heterogeneity chi-square=17.81 df=11 p=0.09 I^2 =38.2%					
Test for overall effect z=2.13 p=0.03					
02 Number of patients vomiting					
Abdel-Ghaffar 1998	1/41	0/20		1.9	1.50 [0.06, 35.27]
Adriaenssens 1999	1/15	2/15		5.6	0.50 [0.05, 4.94]

0.01 0.1 1 10 100

Favours treatment Favours control

(*Continued* . . .)

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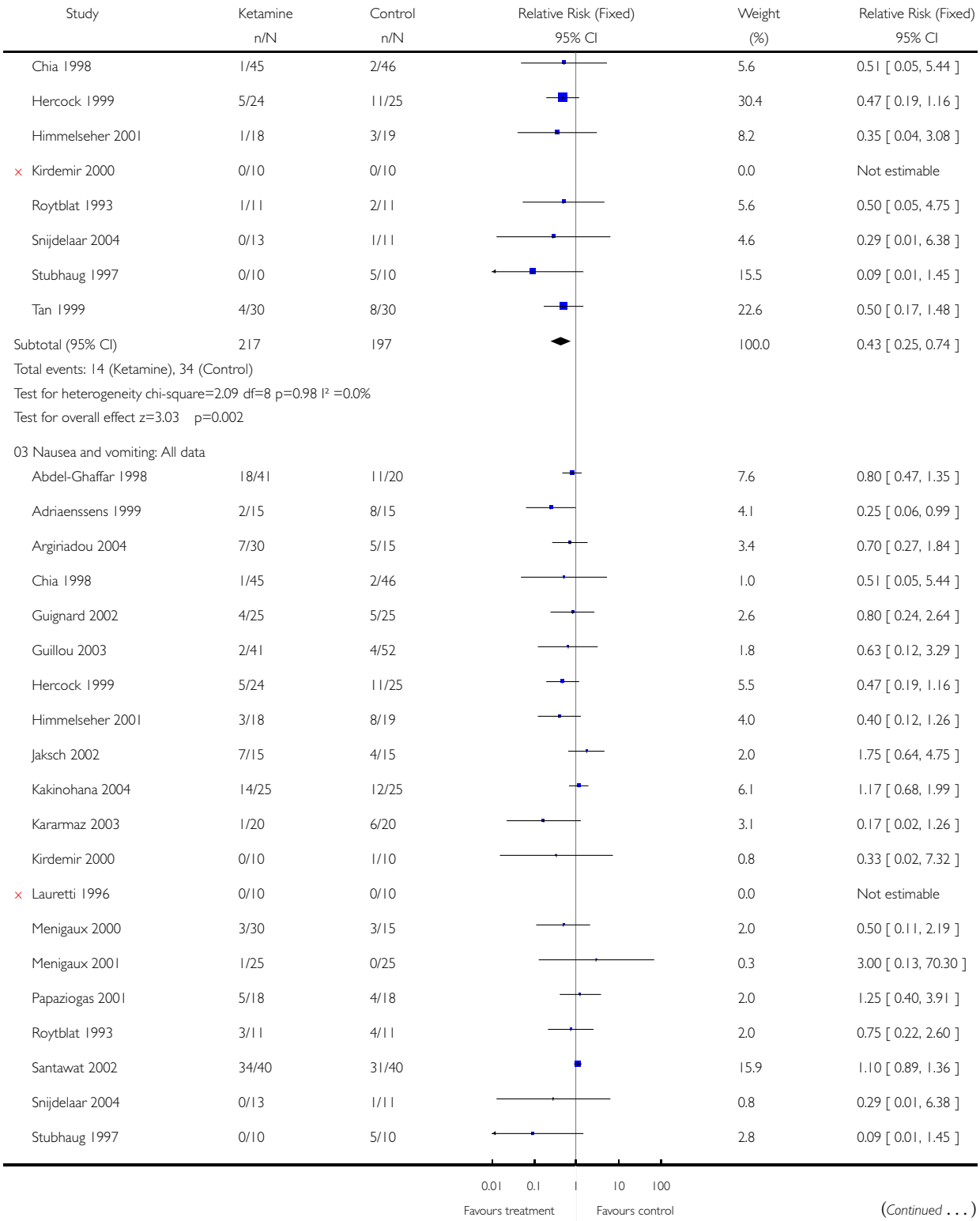

(*Continued* . . .)

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Study	Ketamine n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subramaniam 2001(a)	11/26	11/24		5.9	0.92 [0.49, 1.72]
Subramaniam 2001(b)	3/20	3/20		1.5	1.00 [0.23, 4.37]
Suzuki 1999	27/105	9/35		6.9	1.00 [0.52, 1.92]
Tan 1999	12/30	19/30		9.7	0.63 [0.38, 1.06]
Xie 2003	5/28	5/14		3.4	0.50 [0.17, 1.44]
Ünlügenc 2003	5/30	9/28		4.8	0.52 [0.20, 1.36]
Subtotal (95% CI)	705	578		100.0	0.77 [0.65, 0.90]
Total events: 173 (Ketamine), 181 (Control)					
Test for heterogeneity chi-square=30.82 df=24 p=0.16 I^2 =22.1%					
Test for overall effect z=3.20 p=0.001					
04 24 hr PCA morphine trials PONV					
Adriaenssens 1999	2/15	8/15		25.3	0.25 [0.06, 0.99]
Guignard 2002	4/25	5/25		15.8	0.80 [0.24, 2.64]
Guillou 2003	2/41	4/52		11.1	0.63 [0.12, 3.29]
Jaksch 2002	7/15	4/15		12.6	1.75 [0.64, 4.75]
Roytblat 1993	3/11	4/11		12.6	0.75 [0.22, 2.60]
Snijdelaar 2004	0/13	1/11		5.1	0.29 [0.01, 6.38]
Stubhaug 1997	0/10	5/10		17.4	0.09 [0.01, 1.45]
Subtotal (95% CI)	130	139		100.0	0.61 [0.37, 1.01]
Total events: 18 (Ketamine), 31 (Control)					
Test for heterogeneity chi-square=8.27 df=6 p=0.22 I^2 =27.5%					
Test for overall effect z=1.94 p=0.05					

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Review Article

Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review)

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Background: Post-operative pain management is usually limited by adverse effects such as nausea and vomiting. Adjuvant treatment with an inexpensive opioid-sparing drug such as ketamine may be of value in giving better analgesia with fewer adverse effects. The objective of this systematic review was to evaluate the effectiveness and tolerability of ketamine administered peri-operatively in the treatment of acute post-operative pain in adults.
Methods: Studies were identified from MEDLINE (1966–2004), EMBASE (1980–2004), the Cochrane Library (2004) and by hand searching reference lists from review articles and trials. The manufacturer of ketamine (Pfizer AS, Lysaker, Norway) provided search results from their in-house database, PARDLARS. Randomized and controlled trials (RCTs) of adult patients undergoing surgery, being treated with peri-operative ketamine, placebo or an active control were considered for inclusion.
Results: Eighteen trials were excluded. Thirty-seven trials were included. Twenty-seven out of 37 trials found that peri-operative ketamine reduced rescue analgesic requirements or pain intensity, or both. Quantitative analysis showed that treatment with ketamine reduced 24-h patient-controlled analgesia (PCA) morphine consumption and post-operative nausea and vomiting (PONV). Adverse effects were mild or absent.
Conclusion: In the first 24 h after surgery, ketamine reduces morphine requirements. Ketamine also reduces PONV. Adverse effects are mild or absent. These data should be interpreted with caution as the retrieved studies were heterogenous and the result of the meta-analysis can not be translated into any specific administration regimen with ketamine.

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Key words: ketamine; post-operative pain; meta-analysis.

ADVERSE effects such as nausea and vomiting often limit post-operative pain management. Adjuvant treatment with opioid-sparing drugs such as ketamine may be of value in giving better analgesia with fewer adverse effects (1).

Ketamine is a phencyclidine derivative developed in the 1960s as a general anaesthetic. Ketamine hydrochloride is given intravenously or intramuscularly for surgical anaesthesia. Ketamine is also used as an adjuvant to opioids in the treatment of refractory pain in cancer patients (2), in the treatment of neuropathic pain (3), and in the treatment of acute post-operative pain (1), although not licensed for these conditions. For post-operative pain, ketamine may be administered before incision, after incision, or in the post-operative period, and is usually given as an adjuvant to systemic opioid, for example PCA (patient-controlled analgesia). Routes of administration include intravenous, subcutaneous, epidural, transdermal and intra-articular. Ketamine was previously only available as a racemic mixture of two enantiomers, S(+) and R(–) ketamine. The S(+) isomer has been shown to be approximately twice as potent as the racemic mixture (4). S(+) ketamine has recently been approved for clinical use in countries such as Finland and Germany. Clinical use of ketamine is limited due to psychotomimetic adverse effects such as hallucinations and bad dreams. Other common adverse effects are dizziness, blurred vision, and nausea and vomiting.

Opioids are traditionally used as a part of general anaesthesia and for the treatment of acute post-operative pain. Recent research indicates that

opioids produce not only analgesia, but also hyperalgesia (5). Consequently, peri-operative (pre-, per-, and post-operative) opioids may increase post-operative pain and opioid requirements (6). Central sensitization includes an altered processing of innocuous, tactile impulses from myelinated afferents so that activation of these fibres produces painful sensations (7). The neurophysiological and biochemical mechanisms of these alterations include a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, mediated by wind-up and neurokinin and *N*-methyl-D-aspartic acid (NMDA) receptor mechanisms (7). 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. In animal studies, blockade of NMDA receptors has been shown to prevent the development of increased pain sensitivity and opioid tolerance (5, 8). Ketamine is a non-competitive NMDA receptor antagonist. NMDA receptor blocking could be a fruitful therapy for improving post-operative opioid effectiveness. Ketamine could, in addition to having an opioid-sparing effect, conceivably reduce the development of chronic post-operative pain through NMDA receptor blockade and reduction of wind-up and central sensitization.

Published literature indicates that ketamine is used in the peri-operative setting in countries such as Greece, Brazil, India, Germany, UK, Israel, France, China, Denmark, Norway, and Japan for anaesthesia or as an adjuvant analgesic. However, current use of ketamine in this setting involves different practice regarding dose, route of administration and time of administration. A literature review based on an electronic search of the MEDLINE database from 1966 to 1998 (1) concludes that the role of ketamine remains controversial, but that low-dose ketamine (defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route) as an adjuvant to opioids or local anaesthetics may have an important role to play in the treatment of acute post-operative pain. This review will consider the evidence for the efficacy and tolerability of ketamine in the treatment of acute post-operative pain in adults.

Methods

Search

To identify studies for inclusion in this review, detailed search strategies were developed for each electronic database searched. These searches were based on the search strategy developed for the Cochrane Central Register of Controlled Trials (CENTRAL) and revised appropriately for each database. The subject search used a combination of controlled vocabulary and free text terms and was performed in the Cochrane Pain, Palliative & Supportive Care Register (current issue), the Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library (June 2004), MEDLINE (1966 to June 2004), EMBASE (1980 to June 2004) and PARDLARS (Pfizer Corporation's in-house database) February 2003.

Reference lists of reports and reviews were also searched. Abstracts and unpublished reports were not considered. There was no language restriction.

Inclusion criteria

Randomized, placebo-controlled trials described as double-blinded were included. Trials using active controls in addition to placebo arms were also included. Studies where ketamine was compared with placebo or active control, and each group had a minimum of 10 patients who had completed the study, were included. All identified published trials were considered eligible. Only complete studies, not abstracts, were included. Duplicate publications are reported but excluded from the analysis.

The population addressed by the review is patients aged 18 years or above, undergoing a surgical procedure.

The intervention considered by this review is treatment with ketamine, given systemically or spinally, in any dose during the peri-operative period.

Data extraction and analysis

A data extraction form was designed and the following data items were collected: (i) publication details, (ii) patient population, number of patients, age, surgical procedure, (iii) description of intervention, (iv) design, study duration and follow-up, (v) outcome measures, (vi) analgesic outcome results and (vii) withdrawals and adverse effects.

Study quality (randomization/allocation concealment; details of blinding measures (9, 10); withdrawals and dropouts; overall quality score) were evaluated using the three-item (1–5) Oxford Quality scale (11). Validity was evaluated using the five-item (1–16) Oxford Pain Validity Scale (OPVS) (12). Scoring was performed independently by two reviewers (R.F.B., E.K.). In the case of discrepancy, a third reviewer (J.B.D.) was consulted.

Both dichotomous and continuous data were extracted. Heterogeneity tests were not used as they have previously been shown to be unhelpful (13, 14) although clinical homogeneity was examined visually (15). Meta-analysis was performed where appropriate. The data did not permit calculation of odds ratios, numbers needed to treat (NNTs) and numbers needed to harm (NNHs) with 95% confidence intervals. Continuous data were analysed as weighted mean differences (WMD).

Subgroup analysis was not possible due to the heterogeneity of the trials.

QUOROM guidelines for reporting meta-analyses were followed (16).

Results

The searches identified a total of 165 possible titles. Seventy-three were excluded. Eighteen were not clinical trials. Thirty-eight were abstracts. Thirteen trials did not concern post-operative pain. One was a retrospective study. One paper (17) was irretrievable. Two were duplicates (18, 19). In addition, eight trials were not randomized and 15 did not have an appropriate control. Fourteen trials were not described as double-blind. A total of 55 randomized, controlled, double-blind clinical trials of peri-operative administration of ketamine for post-operative pain control were identified. Eighteen trials were excluded: five due to the administration form of ketamine (two transdermal, two intra-articular, one wound instillation). Four trials were excluded because groups contained less than the minimum of 10 patients who had completed the study. Nine trials (20–28) were excluded due to methodological flaws. The reasons for exclusion were as follows: Clausen (20) (drugs randomized, not patients/inappropriate pain scale); Heinke (21) (primary outcome PCA piritramide consumption/fixed maximum dose of piritramide); Joachimsson (22) (inappropriate pain scale, patients on ventilator); Reeves (23) (different PCA settings); Sadove (24) (inappropriate pain scale); Taura (25) (unclear blinding, different doses of morphine); Weinbroum (26) (flawed randomization); Wong (27) (all patients pre-treated with ketamine); Ünlügenc (28) (different PCA settings).

Thirty-seven trials (29–65) with 53 treatment arms met the inclusion criteria. One study in Turkish (62) was assessed with the help of a native speaker.

Description of studies

These 37 trials with 53 treatment arms could be divided into:

(a) 13 treatment arms with a pre-incisional intravenous or intramuscular bolus of ketamine compared with placebo;
(b) seven treatment arms with an intravenous-bolus of ketamine at wound closure compared with placebo;
(c) 13 treatment arms with a peri-operative continuous infusion/repeated boluses of intravenous ketamine compared with placebo;
(d) seven treatment arms with administration of a pre-incisional bolus of epidural ketamine;
(e) three treatment arms with administration of a post-incisional bolus of epidural ketamine;
(f) two treatment arms with administration of a continuous peri-operative epidural infusion of ketamine compared with placebo;
(g) two treatment arms with intra-operative intravenous ketamine vs. placebo combined with post-operative PCA ketamine/morphine vs. PCA morphine;
(h) four treatment arms with post-operative intravenous PCA ketamine/morphine, compared with intravenous PCA morphine; and
(i) two treatment arms with patient-controlled epidural analgesia (PCEA) ketamine + morphine (and other drugs), compared with PCEA morphine (and other drugs).

Twenty-six trials had a placebo control while 11 used morphine as a control. A total of 2137 patients, of which 1210 received ketamine, were studied. Pain was rated using a visual analogue scale (VAS) in 34 trials, and using a verbal rating scale (VRS) in three.

The most common route of administration of ketamine was intravenous, as a bolus and/or infusion. In six trials, ketamine was administered as an epidural bolus. PCA ketamine was used in four studies and PCEA ketamine in two. Thirty-two trials used racemic ketamine, four trials used S(+) ketamine and one trial used the R(–) isomer.

Quality and validity scores were generally high with a mean quality score of 3.9 and a mean validity score of 10.3. Three trials were considered non-sensitive (41, 50, 53, see Tables 1,3,8). Sensitivity was judged according to criteria in the OPVS.

(a) Studies with administration of a pre-incisional intravenous or intramuscular bolus of ketamine compared with placebo [13 treatment arms, n (ketamine treated) = 266]

Twelve trials with 13 treatment arms compared a pre-incisional bolus dose of ketamine with placebo (Table 1). R(–) ketamine was used in one treatment arm (50), S(+) ketamine in one treatment arm (32) and racemic ketamine in 11 treatment arms.

Table 1

Studies (treatment arms) with administration of a pre-incisional intravenous (i.v.) or intramuscular (i.m.) bolus of ketamine compared with placebo

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Pre-incisional bolus of ketamine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
55	3/11	Open cholecystectomy	11/11	0.15 mg/kg i.v.	PCA-morphine 0–24 h post-op.;Cumulated morphine 0–24 h post-op.	VAS at 0, 1, 2, 3, 4, 5, 6, 12, and 24 h post-op.	Morphine consumption reduced from 48.7 to 29.5 mg, $P < 0.001$	VAS reduced at 0, 1, 2, 3, 4 h post-op. ($P < 0.02$), but not at 5, 6, 12, and 24 h post-op.	
51	5/12	Anterior cruciate ligament repair	15/15	0.15 mg/kg i.v.	PCA-morphine 0–24 h post-op.; Cumulated morphine 0–24 h post-op.	VAS at 0, 1, 2, 3, 7, 11, 15 and 24 h post.op.; VRS at 24 h post-op.	Morphine consumption reduced from 49.7 to 28.2 mg, $P < 0.01$	NS	See also Table 2
49	4/12	Elective laparoscopic or proctologic surgery	40/40	0.15 mg/kg i.v.	PCA-piritramide 0–24 h post-op.; Cumulated piritramide 0–24 h post-op.	VAS and VRS at 1, 2, 3, 4, 5, 6, 12, 24 h post-op.	NS	NS	
50	5/11	Laparoscopic cholecystectomy	20/20	1 mg/kg i.v. R (-) ketamine	PCA-meperidine 0–4 h post-op. and paracetamol 500 mg + codeine 30 mg 4-24 h post-op.; Cumulated meperidine 0-4 h post-op. and no of doses of paracetamol/codeine 4–24 h post-op.	VAS at 30 min, and at 1, 2, 3 and 4 h post.op.; VRS at 24 h and 7 d post-op.	NS	NS	See also Table 2 Insensitive study. All patients received pre-treatment with i.v. ketorolac and pre-incisional skin infiltration with bupivacaine. All patients received paracetamol 1000 mg at arrival in the recovery room
48	2/8	Vaginoplasty	10/10	0.2 mg/kg i.v.	i.m. diclofenac 75 mg on patient request; No of doses of diclofenac 0–24 h post-op.	Overall VAS 0–24 h post-op.	Diclofenac consumption reduced from 3.7 to 2.1 doses, $P < 0.05$	NS	('Ketamine group vs. Control group', see original paper)
48	2/8	Vaginoplasty	10/10	(see 48)	(see 48)	(see 48)	Diclofenac consumption reduced from 3.1 to 1.5 doses, $P < 0.05$	NS	('Ketamine neostigmine group vs. Neostigmine control group", see original paper) Both study groups received neostigmine intrathecally 50 μg
35	4/13	Abdominal hysterectomy	33/29	0.4 mg/kg i.v.	i.v.-ketobemidone in incremental doses of 1 mg when VAS > 30; mg ketobemidone at 0–6, 6–24 h post-op.	VAS and VRS 0–6, and 6–24 h post-op.	NS	NS	See also Table 2 All patients received supp. paracetamol 1000 mg three times daily
52	5/14	Arthroscopic knee surgery morphine	25/25	0.15 mg/kg i.v.	i.v.-morphine in incremental doses of 3 mg until VAS ≤ 30 or VRS < 2; No of patients receiving morphine	VAS at 15, 30, 45 min, and at 1, 2, 4 and 6 h post-op.	No of patients requiring morphine reduced from 9 to 3, $P < 0.05$	VAS reduced from 0-6 h post-op., $P < 0.01$	Oral naproxen sodium 550 mg given to all patients post-operatively

54	3/9	Laparoscopic cholecystectomy	18/18	1 mg/kg i.v.	Supp. diclofenac 50-100 mg if VAS $>$ 30, parenteral dextropropoxyphene if pain persisted, meperidine 50 mg i.m. if pain relief with dextropropoxyphene not adequate; Doses of analgesics 0-48 h post-op.*	VAS at 0, 3, 6, 12, and 24 h post-op.	NS	VAS reduced at 6 and 12 h post-op. ($P < 0.01$), but not at 0, 3, 24 h post-op.	*Data from 0-24 h could not be extracted
32	4/9	Major abdominal	15/15	0.5 mg/kg i.v. S(+) ketamine	If VAS $>$3, diclofenac supp. If pain persisted 30 min after diclofenac, i.v. dextropropoxyphene titrated until VAS $<$2; Cumulative consumption of diclofenac and dextropropoxyphene	VAS on awakening, 3, 6, 24 h	Cumulative consumption of rescue analgesics reduced $P < 0.05$	NS	
47	5/16	Laparoscopic gynaecological	45/45	0.15 mg/kg i.v.	i.v. morphine 1.5 mg every 5 min until comfortable or VAS $\leq$ 20 mm. On ward, i.m. morphine 0.15 mg/kg every 4 h or 1-2 tbs. paracetamol/ dextropropoxyphene every 6 h, as required; Analgesic consumption	VAS at 15, 30, 45 and 60 min, then at 2, 4, 6, 24 h	Mean total morphine consumption reduced from 3.4 mg to 1.5 mg $P = 0.003$	VAS reduced at 15, 30, 45, 60 min, 2, 4, 6 h $P < 0.001$	Patients were interviewed for up to 7 days after surgery
62	3/10	Thoracotomy	10/10	1 mg/kg i.m.	PCEA (bupivacaine 1.25% + morphine 0.075 mg/ml) loading dose 5 ml, bolus 5 ml, lockout 30 min Post-op. PCEA opioid and local anaesthetic consumption	VAS at 2, 4, 6, 12, 24, 48 h	NS	VAS reduced 0- 12 h	
64	4/9	Selective gastrectomy	14/14	0.5 mg/kg i.v.	PCEA morphine 0–48 h post-op. Morphine consumption 0–48 h post-op.*	VAS at 2, 4, 8, 12, 24, 36, 48 h	48-h morphine consumption reduced $P < 0.01$	VAS reduced at 4, 8, 12 ($P < 0.01$) and 24 h ($P < 0.05$)	*Data from 0–24 h post-op. could not be extracted – pain and morphine consumption was followed for 48 h post-op.

*Only data from the first 24 post-operative hours are included.

The retrieved trials were heterogeneous. The doses of ketamine varied almost sevenfold, from 0.15 to 1.0 mg/kg intravenously. Different analgesics and treatment regimens were employed for rescue medication, and the surgical procedures included various gynaecological, abdominal, and orthopaedic operations. Due to this disparity, a meta-analysis of the combined results was not considered rational.

In one of these trials having two treatment arms, one pre- and one post-incisional, all patients had been pre-treated with intramuscular ketorolac together with pre-incisional skin infiltration with bupivacaine (50). This trial was scored as non-sensitive.

Post-operative analgesic requirements were reduced by a pre-incisional ketamine bolus in eight out of 13 treatment arms. VAS pain scores were reduced for up to 24 h post-operatively in seven of the 13 arms.

(b) Studies with administration of an intravenous-bolus of ketamine at wound closure compared with placebo [seven treatment arms, n (ketamine treated) = 212]

Five trials with seven treatment arms compared a post-incisional bolus dose of ketamine with placebo (Table 2). R(–) ketamine was used in one (50) and racemic ketamine in six treatment arms.

Again the trials were heterogenous and involved such different surgical procedures as elective outpatient surgery and abdominal hysterectomy. Ketamine doses ranged from 0.05 to 1 mg/kg. Two studies (50, 51) used PCA opioid for post-operative pain and three studies used an incremental intravenous-opioid bolus on request.

In three out of seven treatment arms, post-operative morphine requirements were reduced by post-incisional ketamine. VAS pain scores were reduced in four out of seven treatment arms.

(c) Studies with administration of a peri-operative continuous infusion/repeated boluses of intravenous-ketamine compared with placebo [13 treatment arms, n (ketamine treated) = 290]

Eleven trials with 13 treatment arms compared a peri-operative continuous intravenous infusion/repeated intravenous bolus of ketamine with placebo (Table 3). A ketamine infusion was used in 12 treatment arms and a repeated intra-operative bolus of ketamine at 20-min intervals in one (32). S(+) ketamine was used in two treatment arms (32, 42) and racemic ketamine in 11.

The surgical procedures varied and included predominantly major abdominal and renal surgery. There was clinical heterogeneity, with wide variation in the total ketamine dose administered due to different doses and duration of infusions. Different analgesics and treatment regimens were employed for rescue medication.

In one treatment arm, all patients received epidural bupivacaine 2.5 mg/ml, 4 ml/h for 0–24 h post-operatively (41). This was a trial with a negative outcome and was considered potentially non-sensitive. However, as the patients experienced pain above 30 on the VAS during movement in the early post-operative period, and to avoid bias, the trial was included in the quantitative analysis.

Ketamine treatment reduced post-operative analgesic requirements in nine out of 13 treatment arms. VAS pain scores were reduced in seven out of 13 treatment arms.

(d) Studies with administration of a pre-incisional bolus of epidural ketamine [eight treatment arms, n (ketamine treated) = 119]

Seven trials with seven treatment arms investigated a pre-incisional epidural bolus of ketamine (Table 4). Two trials with two treatment arms investigated a pre-incisional epidural bolus of ketamine and morphine compared with morphine alone. Racemic ketamine was used in six treatment arms, while S(+) ketamine was used in one (40). These trials concerned major surgical procedures such as total abdominal hysterectomy, colectomy, gastrectomy and total knee arthroplasty. The ketamine doses varied from 0.25 to 1 mg/kg.

Consumption of rescue analgesics was reduced in only two out of seven treatment arms.

Pain scores were reduced in three out of seven treatment arms. One trial did not provide pain score data (59).

(e) Studies with administration of a post-incisional bolus of epidural ketamine [three treatment arms, n (ketamine treated) = 61]

Three trials with three treatment arms investigated a post-incisional epidural bolus of ketamine (Table 5) Two trials investigated epidural ketamine + morphine, compared with epidural morphine alone (56, 60). One trial compared epidural ketamine with placebo (29). All trials used racemic ketamine. Two trials used a ketamine dose of 30 mg while the third trial used a dose of 1 mg/kg.

Analgesic consumption was reduced in two out of three treatment arms. Two treatment arms found no difference in pain scores. The third trial (60) did not provide pain score data.

Table 2

Studies (treatment arms) with administration of an i.v. bolus of ketamine at wound closure compared with placebo. Only data from the first 24 postoperative hours included

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. bolus of ketamine at wound closure	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
51	5/12	Anterior cruciate ligament repair	15/15	0.15 mg/kg	PCA-morphine 0–24 h post-op.; Cumulated morphine 0–24 h post-op.	VAS at 0, 1, 2, 3, 7, 11, 15 and 24 h post-op.; VRS at 24 h post-op.	Morphine consumption reduced from 49.7 to 24.2 mg, $P < 0.01$	NS	See also Table 1
50	5/11	Laparoscopic cholecystectomy	20/20	1 mg/kg R (-) ketamine	PCA-meperidine 0–4 h post-op. and paracetamol 500 mg + codeine 30 mg 4–24 h post-op.; Cumulated meperidine 0–4 h post-op. and No of doses of paracetamol/ codeine 4–24 h post-op.	VAS at 30 min, and at 1, 2, 3 and 4 h post-op.; VRS at 24 h post-op.	NS	VAS reduced at 30 min post-op. ($P < 0.05$), but not at 1, 2, 3 and 4 h post-op.; VRS NS at 24 h post-op.	See also Table 1 Insensitive study. All patients received pre-treatment with i.v. ketorolac and pre-incisional skin infiltration with bupivacaine. All patients received paracetamol 1000 mg at arrival in the recovery room
35	4/13	Abdominal hysterectomy	27/29	0.4 mg/kg	i.v. ketobem-idone in incremental doses of 1 mg when VAS > 30; mg ketobemidone at 0–6, 6–24 h post-op.	VAS and VRS 0-6 and 6-24 h post-op.	NS	VAS and VRS reduced from 0–6 h post-op. ($P < 0.05$), but not from 6–24 h post-op.	See also Table 1 All patients received supp. paracetamol 1000 mg three times daily
61	5/15	'Elective outpatient surgery'	35/35	0.05 mg/kg	i.v. morphine in incremental doses of 2 mg on patient request; Cumulated morphine	VAS at 0, 15, 30, 45 min post-op.	NS	NS	Duration of treatment not clear, but approx. 60 min

Table 2 Continued

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. bolus of ketamine at wound closure	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
61			35/35	0.075 mg/kg			Morphine consumption reduced $P < 0.05$	VAS reduced from 0–45 min post-op. ($P < 0.0001$)	
61			35/35	0.1 mg/kg			Morphine consumption reduced $P < 0.05$	VAS reduced from 0–45 min post-op. ($P < 0.0001$)	
47	5/16	Gynaecological laparoscopic	45/45	0.15 mg/kg	i.v. morphine 1.5 mg every 5 min until comfortable or VAS $\leq$ 20 mm. On ward, i.m. morphine 0.15 mg/kg every 4 h or 1-2 tbs. paracetamol/ dextropropoxyphene every 6 h, as required; Analgesic consumption	VAS at 15, 30, 45 and 60 min, then at 2, 4, 6, 24 h	NS	NS	Patients were interviewed for up to 7 days after surgery

(f) Studies with administration of a continuous peri-operative epidural infusion of ketamine compared with placebo [two treatment arms, n (ketamine treated) = 40]

One trial with two treatment arms (36) investigated an epidural bolus of ketamine followed by an epidural infusion of ketamine until the end of surgery, compared with a control group (no ketamine) (Table 6). This trial used racemic ketamine at a dose of 0.25 mg/kg bolus + 0.125 mg/kg/h in one treatment arm and 0.5 mg/kg and 0.25 mg/kg/h in the other.

There was no significant difference in post-operative analgesic consumption or pain scores.

(g) Studies with intra-operative intravenous ketamine vs. placebo combined with post-operative PCA ketamine/ morphine vs. PCA morphine [two treatment arms, n (ketamine treated) = 37]

Two trials with two treatment arms investigated intra-operative intravenous ketamine combined with post-operative PCA ketamine + morphine, compared with per-operative placebo and post-operative PCA morphine (Table 7). S(+) ketamine was used in one trial (57) and racemic ketamine in the other (38).

Cumulative morphine consumption and pain scores at rest were reduced in one treatment arm (57).

(h) Studies with post-operative intravenous PCA ketamine/ morphine, compared with intravenous PCA morphine [four treatment arms, n (ketamine treated) = 110]

Four trials with four treatment arms investigated post-operative intravenous PCA ketamine + morphine, compared with intravenous PCA morphine (Table 8). Racemic ketamine was used in all trials. Doses ranged from 0.75 to 2 mg/ml. One trial was judged to be potentially non-sensitive as 60–70% of the patients were pain free for the first 4 h after surgery (53).

Morphine consumption was reduced in two out of four treatment arms. Pain scores were reduced in three out of four treatment arms.

(i) Studies with PCEA ketamine + morphine (and other drugs), compared with PCEA morphine (and other drugs) [two treatment arms, n (ketamine treated) = 75]

Two trials with two treatment arms investigated PCEA ketamine + morphine, compared with PCEA morphine (Table 9). These studies were performed in patients undergoing major thoracic or abdominal surgery. Racemic ketamine was used in both treatment arms.

Table 3

Studies (treatment arms) with administration of a peri-operative continuous infusion/ repeated boluses of i.v. ketamine compared with placebo

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. ketamine bolus/infusion	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
37	3/9	Open colorectal surgery	25/25	0.15 mg/kg before surgical incision/ 2 μg/ kg/min until skin closure	Nurse-administration of i.v. morphine in incremental doses of 3 mg until VAS < 10 or VRS < 2, followed by PCA-morphine until 24 h post-op.; Cumulated nurse-administered morphine and cumulated PCA-morphine until 24 h post-op.	VAS and VRS 0–24 h post-op.	Nurse-administered morphine: NS PCA-morphine reduced from 69 to 46 mg	NS	
31	3/8	Gastrectomy	29/31	1 mg/kg before surgical incision/ 0.5 mg/kg/h until skin closure	Epidural PCA-morphine 0–24 h post-op.; Cumulated morphine 0–6, 0–12, and 0–24 h post-op.	VAS at 6, 12, and 24 h post-op.	Epidural PCA-morphine reduced at all periods. Reduced from 7.2 to 6 mg from 0–24 h post-op. ($P < 0.05$)*	VAS reduced at 6, 12, and 24 h post-op. ($P < 0.05$)	('KETiv vs. CTL', see original paper). * = median values read from figures
31	3/8	Gastrectomy	31/31				Epidural PCA-morphine reduced at all periods. Reduced from 5 to 0 mg from 0–24 h post-op. ($P < 0.05$)*	VAS reduced at 6, 12 and 24 h post-op. ($P < 0.05$)	('COMB vs. MORep', see original paper) Both study groups received epidural morphine (bolus 0.06 mg/kg – cont. infusion 0.02 mg/kg/h) * = median values read from figures

Table 3 Continued

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. bolus of ketamine at wound closure	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
42	4/13	Arthroscopic anterior cruciate ligament repair	15/15	0.5 mg/kg before surgical incision/ 2 μg/ kg/min until 2 h post-op. S(+) ketamine	Nurse-administration of i.v. morphine in incremental doses of 2 mg if VAS $>$ 30, followed by PCA-morphine from 1–24 h post-op.; Cumulative PCA-morphine 0–24 h post-op.	VAS at 1, 2, and 24 h post-op.	NS	NS	All patients received lornoxicam 8 mg at 15 min before wound closure; Patients were followed for 120 h post-op.
58	5/12	Donor nephrectomy	10/10	0.5 mg/kg before surgical incision/ 2 μg/ kg/min until 24 h post-op.	PCA-morphine from 0–24 h post-op.; Cumulative PCA-morphine 0–24 h post-op.	VAS at 1, 2, 3, and 4 h post-op.	PCA-morphine reduced from 0–6 h post-op. ($P < 0.05$), but not from 0–24 h post-op.	VAS reduced at 1 h post-op. ($P < 0.05$), but not at 2, 3, and 4 h post-op.	All patients received intercostal nerve blockades with bupivacaine 5 mg/ml, 20 ml before wound closure; Ketamine infusion continued for 72 h post-op.; Patients were followed for 7 days post-op.
41	4/11	Nephrectomy/ Hynes Anderson	24/28	10 mg before surgical incision/ 10 mg/h for 24 h post-op.	PCA-morphine from 0–24 h post-op.; Cumulative PCA-morphine 0–24 h post-op.	VAS at 4, 6, 8, 22 and 24 h post-op.	NS	NS	Insensitive study. All patients received epidural bupivacaine 2.5 mg/ml, 4 ml/h, from 0–24 h post-op.; Ketamine infusion continued, and patients were followed for 48 h post-op.
30	2/6	Laparotomy (gastrointestinal, urological, gynaecological)	15/15	After surgery: No bolus/initial infusion rate 10 μg/kg/min, reduced to 2.5 μg/kg /min after 45 min, continued for 24 h post-op.	PCA-morphine from 0–24 h post-op.; Cumulative PCA-morphine 0–24 h post-op.	VAS at 0, 1, 2, 4, 6, 12, and 24 h post-op.	PCA-morphine reduced from 30.7 to 19.4 mg from 0–24 h post-op. ($P = 0.03$)	VAS reduced at 1 h post-op. ($P = 0.01$), but not at 0, 2, 4, 6, 12 and 24 h post-op.	Ketamine infusion continued, and patients were followed for 48 h post-op.

32	4/9	Major abdominal	15/15	Pre-incisional 0.5 mg//kg bolus S(+) ketamine + intra-operative 0.2 mg/kg at 20-min intervals until the end of surgery S (+) ketamine	If VAS >3, diclofenac suppl. If pain persisted 30 min after diclofenac, i.v. dextropropoxy-phene titrated until VAS < 2 Cumulative consumption of diclofenac and dextropropoxyphene	VAS on awakening, 3, 6, 24 h	Cumulative consumption of rescue analgesics at 24 h reduced $P < 0.05$	VAS reduced at 0, 3, 6 h $P \leq 0.05$	
36	5/14	Rectal adenocarcinoma surgery	20/20	± 30 min before skin incision: 0.25 mg/kg bolus + infusion 0.125 mg/kg/h until the end of surgery	After recovery of awareness: PCA-morphine from 0–24 h post-op. Cumulative number of met and unmet PCA morphine demands	VAS at 15 min, 2, 6, 12, 24 h post-op. Area of hyperalgesia. Post-operative residual pain at 2 weeks, 1 month, 6 months, 1 year	NS	NS	PCA morphine: max. allowed dose: 30 mg/h. PCA and observations for 48 h post-op. Long-term follow-up re-wound mechanical hyperalgesia and residual pain. All patients received a continuous peroperative epidural infusion of bupivacaine/ sufentanil/clonidine
36			20/20	± 30 min before skin incision: 0.5 mg/kg bolus + infusion 0.25 mg/kg/h until the end of surgery			NS	NS	Area of hyperalgesia reduced $P < 0.05$ Reduced residual pain for up to 6 months $P < 0.05$
38	4/12	Major abdominal	41/52	After surgery: initial bolus 0.5 mg/kg, infusion 2 μg/kg/ min for 24 h and 1 μg/kg/min from 24–48 h	PCA morphine from 0–24 h; Cumulative dose of morphine 0–24 h (4-hourly intervals)	VAS at 0, 4, 8, 12, 16, 20, 24 h	Morphine consumption significantly reduced at all time intervals $P < 0.05$	NS	VAS and morphine consumption assessed for 48 h post-op.

Table 3 Continued

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. bolus of ketamine at wound closure	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
44	3/11	Elective open cholecystectomy	25/25	Pre-incisional 1 mg/kg bolus + 1 mg/kg/h peroperative infusion, maintained until 2 mg/kg given	2 mg morphine ED + bupivacaine post-op. Thereafter PCEA bupivacaine + morphine. PCEA volume consumed at 5, 24 and 48 h	VAS at 5, 24 and 48 h	Mean PCEA consumption reduced at 5 and 5–24 h	VAS scores reduced at all time points: Mean VAS rest at 5 h reduced from 3.5 to 1.1 $P < 0.01$ VAS movement 5 h reduced from 5.9 to 3.7 $P < 0.01$ VAS rest 24 h reduced from 1.5 to 0.6 $P < 0.01$ VAS movement at 24 h reduced from 4.4 to 3.0 $P < 0.01$	VAS and PCEA consumption assessed for 48 h post-op.
45	5/13	Elective renal surgery	20/20	0.5 mg/kg bolus + 0.5 mg/kg/h until skin closure	PCEA morphine and bupivacaine, basal infusion started before incision, stopped at 6 h if VAS < 3. No. of analgesic demands	VAS rest at 0.5, 1, 2, 4, 6, 12, 24 and 48 h VAS coughing at 12, 24, 48 h	Mean PCEA analgesic consumption reduced from 81.6 to 60.3 ml Day 1 $P = 0.001$	VAS rest reduced 0–6 h $P < 0.01$ VAS coughing reduced at all time points $P < 0.01$	VAS and PCEA for 48 h post-op.

Only data from the first 24 post-operative hours included.

Table 4

Studies (treatment arms) with administration of a pre-incisional bolus of epidural ketamine

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Epidural ketamine, bolus	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
46	3/7	Abdominal surgery	10/10	50 mg before surgical incision	Nurse-administration of epidural morphine in incremental doses of 2 mg if VAS $>$ 30; Cumulative epidural morphine 0–48 h post-op.*	VAS at 1, 2, 6, 12, and 24 h post-op.	NS	NS	*No data for cumulative epidural morphine 0–24 h post-op.
40	5/11	Total knee arthroplasty	18/19	0.25 mg/kg before surgical incision [S(+) ketamine]	PCEA ropivacaine, and diclofenac, paracetamol, piritramide if pain persisted; Cumulative PCEA ropivacaine 0–24 h post-op., and cumulative diclofenac, paracetamol, piritramide 0–48 h post-op.	VAS at 2, 4, 6, 8, and 24 h post-op.	NS*	Pain at rest and during movement reduced at 24 h post-op. ($P < 0.05$), but not at 2, 4, 6, 8 h post-op.	*NS at 0–24 h post-op., but cumulative consumption of ropivacaine significantly reduced from 0–48 h in patients receiving ketamine ($P < 0.01$)
29	5/13	Total abdominal hysterectomy	21/20	30 mg before surgical incision	PCEA bupivacaine/ fentanyl; Cumulative PCEA bupivacaine/ fentanyl 0–24 h post-op.	VAS at 1, 2, 4, 8, 12 and 24 h post-op.	PCEA with bupivacaine/ fentanyl reduced from 4-24 h post-op. in patients receiving ketamine ($P < 0.05$)	NS	
56	4/11	Gynaecological surgery	20/20	30 mg before surgical incision	Pethidine 1 mg/kg i.m. if severe pain or oral paracetamol 1000 mg every 6 h is needed. Analgesic consumption.	VAS every 3 h for 48 h post-op.	NS	NS	
59	3/10	Major upper abdominal	26/24	1 mg/kg before surgical incision	ED morphine 50 μg/kg when VAS on deep inspiration $>$ 4. Number of doses.	VAS on deep inspiration at 0, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 h	NS	Not reported	Intra-operative morphine requirements reduced ($P = 0.018$)

Table 4 Continued

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	i.v. bolus of ketamine at wound closure	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
62	3/10	Thoracotomy	10/10	0.5 mg/kg	PCEA (bupivacaine 1.25% + morphine 0.075 mg/ml) loading dose 5 ml, bolus 5 ml, lockout 30 min Post-op. PCEA opioid and local anaesthetic consumption	VAS at 2, 4, 6, 12, 24, 48 h	NS	VAS reduced 0-24 h	
64	4/9	Selective gastrectomy	14/14	0.5 mg/kg	PCEA morphine 0–48 hpost-op. Morphine consumption 0–48 h post-op*	VAS at 2, 4, 8, 12, 24, 36, 48 h	Morphine consumption reduced $P < 0.01$	VAS scores at rest reduced at 4, 8, 12, 24 h $P < 0.01$	*Data from 0–24 h post-op. could not be extracted – pain and morphine consumption was followed for 48 h post-op.

Only data from the first 24 post-operative hours are included.

Analgesic consumption was reduced in both treatment arms. Pain scores were reduced in both treatment arms.

In summary, the need for rescue medication was reduced in 29 out of 53 treatment arms, whereas VAS or VRS pain intensity scores were reduced in 27 out of 51 treatment arms, pain score data not being given in the two remaining arms. No study reported an increased need for rescue medication, or higher VAS scores in the ketamine group.

When individual trials, rather than treatment arms, were examined, 27 out of 37 trials found that peri-operative ketamine reduced rescue analgesic requirements or pain intensity, or both.

Ketamine dose

The question of optimal ketamine dose is not resolved by these heterogenous trials. Out of interest, we wanted to see whether there was a dose-dependent effect. Using an 'average' weight of 70 kg, we roughly calculated the mean 24-h dose of ketamine for each of the trials included in the 24-h PCA morphine meta-analysis. The trials could be divided into four groups: one group with an estimated dose of approximately 10 mg, one group with estimated dose of approximately 30 mg, a third group with estimated dose of approximately 65 mg and a fourth group with estimated dose of 250–270 mg. Interestingly, there seemed to be no increased morphine-sparing effect on increasing the ketamine dose above an estimated dose of 30 mg/24 h.

Adverse effects

Two trials (31, 62) did not report on adverse effects. In general, the occurrence of adverse effects was similar in ketamine- and placebo-treated groups.

Psychotomimetic adverse effects

Twenty-one of 37 trials specifically stated that there were no psychotomimetic adverse effects such as hallucinations, bad dreams or dysphoria. Psychotomimetic adverse effects were reported in four trials (33, 41, 43, 60). Ilkjær et al. (41) reported that two patients in the ketamine group, and one in the placebo group, experienced psychomimetic side-effects. Burstal et al. (33) reported withdrawal of four patients in the ketamine group due to dysphoria. Subramaniam et al. (60) reported one patient developing hallucinations after pre-operative administration of ketamine, but no psychotomimetic

Table 5

Studies (treatment arms) with administration of a post-incisional bolus of epidural ketamine

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Post-incisional bolus of ketamine/ morphine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
29	5/13	Total abdominal hysterectomy	21/20	30 mg 20 min after surgical incision	PCEA bupivacaine/ fentanyl; Cumulative PCEA bupivacaine/ fentanyl 0–24 h post-op.	VAS at 1, 2, 4, 8, 12 and 24 h post-op.	PCEA with bupivacaine/ fentanyl reduced from 4-24 h post-op. in patients receiving ketamine $P < 0.05$	NS	
56	4/11	Gynaecological surgery	20/20	30 mg after surgical incision	Pethidine 1 mg/kg i.m. if severe pain or oral paracetamol 1000 mg every 6 h as needed; Analgesic consumption	VAS every 3 h for 48 h post-op.	NS	NS	
60	4/10	Major upper abdominal surgery	20/20	1 mg/kg post-op.	ED morphine 50μg/kg when VAS > 4; Total no. of doses	VAS during deep inspiration at 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 h	Total no. of morphine doses reduced $P < 0.005$ (only data for 48 h)	Not reported	

Only data from the first 24 post-operative hours included.

adverse effects in the post-operative period. Javery (43) reported one patient in the ketamine group experiencing dysphoria, compared with three in the control group.

Nausea and vomiting

One trial reported significantly less nausea in the ketamine-treated group compared with placebo (30). One trial reported significantly less nausea in the ketamine + morphine-treated group, compared with the morphine group (43). One trial reported significantly less nausea, vomiting and use of antiemetics in the ketamine group on the first post-operative day (58).

Sedation

Four trials (37, 41, 50, 59) reported increased sedation in the ketamine-treated groups: Ilkjær et al. (41) reported significantly higher sedation scores for 0 –24 h after surgery. Guignard et al. (6) reported higher sedation scores for the first 15 min after extubation. Mathisen et al. (50) found that the placebo-treated group opened their eyes significantly faster and were extubated earlier than the R(–) ketamine-treated groups. Subramaniam et al. (59) reported high sedation scores in six patients in the ketamine group, compared with none in the control group, for the first 2 h after surgery, but no difference thereafter.

Diplopia

Diplopia as an adverse effect of ketamine was reported in three trials (30, 42, 45). Adriaenssens (30) reported that two out of 15 ketamine-treated patients experienced diplopia, while Jaksch (42) reported diplopia in one out of 15 patients in the ketamine group. Kararmaz (45) reported diplopia in three ketamine-treated patients, compared with none in the control group.

Quantitative data synthesis

The data did not permit the calculation of odds ratios, numbers-needed-to-treat (NNTs) or numbers-needed-to-harm (NNHs).

Meta-analysis of studies employing post-operative PCA-morphine

Twelve trials (30, 36–38, 41–43, 51, 53, 55, 57, 58) provided data on 24-h cumulative intravenous PCA morphine consumption. The authors of nine trials were contacted in order to get the data

Table 6

Studies (treatment arms) with administration of a continuous peri-operative epidural infusion of ketamine compared with placebo

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Continuous pre-operative epidural infusion of ketamine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
36	5/14	Rectal adenocarcinoma surgery	20/20	0.25 mg/kg bolus + 0.125 mg/kg /h until the end of surgery	After recovery of awareness: PCA-morphine from 0–24 h post-op; Cumulative number of met and unmet PCA morphine demands	VAS at 15 min, 2, 6, 12, 24 h post-op. Area of hyper-algesia. Post-operative residual pain at 2 weeks, 1 month, 6 months, 1 year	NS	NS	See also Table 3
36			20/20	0.5 mg/kg bolus + 0.25 mg/kg/h until the end of surgery			NS	NS	See also Table 3

Only data from the first 24 post-operative hours included.

expressed as means ± SD. Six authors kindly provided the necessary data. Though the author of one trial (55) could not be contacted, data could be extracted from a figure. In two trials (36, 53) it was not possible to obtain the requested data.

In a total of 10 trials with 11 treatment arms and a total of 432 patients, treatment with ketamine significantly reduced PCA morphine consumption in the first 24 h after surgery [WMD −15.98 mg with 95% CI (−19.70, −12.26)] (Fig. 1).

Meta-analysis of adverse effects with ketamine

Twenty-six out of 37 trials provided dichotomous data on nausea and vomiting, or nausea and/or vomiting. The total number of patients in the comparison was 1261. When all data were combined, treatment with ketamine significantly reduced post-operative nausea and vomiting ($P = 0.001$). When the data for nausea and for vomiting alone were analysed, treatment with ketamine reduced nausea ($P = 0.03$) and vomiting ($P = 0.002$). When the data from trials included in the 24-h PCA morphine consumption analysis were examined separately, ketamine reduced nausea and vomiting ($P = 0.03$) (Fig. 2).

Discussion

The objective of this systematic review was to assess the effectiveness and adverse effects of peri-operative ketamine in the treatment of acute post-operative pain.

Twenty-seven out of 37 trials found that peri-operative ketamine reduced rescue analgesic requirements or pain intensity, or both. Ten trials found no significant difference between ketamine and placebo, three of which were considered non-sensitive.

During the preparation of this review, two systematic reviews investigating ketamine for post-operative pain were published (66, 67). These reviews include trials in children and trials excluded in our own review due to route of administration and/or methodological issues. The authors of the first review (66) included 37 trials. The primary outcome was VAS scores in the first 24 h after surgery. Due to the heterogeneity of the data, we have chosen to restrict quantitative analysis to 24-h PCA morphine consumption and data on PONV.

The second review (67) has similar findings to our own, with ketamine giving a clear decrease in 24-h cumulative morphine consumption with a weighted

Table 7

Studies (treatment arms) with intra-operative i.v. ketamine vs. placebo combined with post-operative PCA ketamine/morphine vs. PCA morphine

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Intra-operative i.v. ketamine post-operative PCA i.v. ketamine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
39	4/10	Total abdominal hysterectomy	24/25	i.v. bolus 0.3 mg/kg after induction/ PCA 1 mg/ bolus	Rescue analgesia in PACU: i.v. morphine 1-2 mg as needed; PCA morphine/ ketamine or PCA morphine; PCA morphine consumption 0–24 h post-op.	VRS at 24 h post-op.	NS	NS	
57	5/11	Radical retropubic prostatectomy	13/12	i.v. bolus 0.1 mg/kg, followed by cont. infusion of 0.002 mg/kg /min until skin closure/ PCA 0.5 mg bolus S(+) ketamine	PCA morphine/ ketamine or PCA morphine; PCA morphine consumption 0–48 h post-op.	VAS rest at 1, 2, 3, 4, 8, 12,18, 24, 30, 36, 42, 48 h post-op.; VAS mobilisation at 24, 48 h post-op.	Cumulative PCA-morphine consumption – 48 h post-op. reduced $P = 0.049$	Cumulative VAS rest from 0–48 h post-op. reduced, $P < 0.01$ VAS mobilisation NS	Data from 0–24 h post-op. could not be extracted – pain and morphine consumption was followed for 48 h post-op.

Only data from the first 24 postoperative hours included.

Table 8

Studies (treatment arms) with post-op. i.v. PCA ketamine/morphine, compared with i.v. PCA morphine

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	Post-op. i.v. PCA ketamine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
33	5/14	Total abdominal hysterectomy	37/33	2 mg/bolus	Bolus dose of morphine given in recovery before PCA. PCA morphine/ ketamine or PCA morphine; PCA morphine consumption 0–48 h post-op. or at cessation of PCA	VAS at rest and on coughing Area of allodynia (Von Frey)	NS	VAS scores on coughing reduced on Day 1. Otherwise NS	Area of allodynia reduced $P = 0.04$ 10 patients in ketamine group vs 1 in control group withdrawn due to adverse effects. All patients included in efficacy analysis
43	2/9	Lumbar micro-discectomy	22/20	1 mg/bolus	PCA morphine/ketamine or PCA morphine; PCA morphine consumption 0–24 h post-op.	VAS at 24 h post-op.	Mean morphine consumption reduced from 51.1 to 25.82 mg ($P < 0.001$)	Mean VAS reduced from 4.5 to 2.3 ($P < 0.001$)	Reduced nausea, pruritus and urinary retention in the ketamine group
53	4/12	Total abdominal hysterectomy	21/21	0.75 mg/bolus	PCA morphine/ ketamine or PCA morphine; PCA morphine consumption 0–24 h post-op.	VRS 4, 8, 12, 16 and 24 h after surgery	NS	NS	Insensitive study PCA background infusion with ketamine 0.75 mg/h/ morphine 1 mg/h or morphine 1 mg/h Single intra-operative dose of ketamine 7.5 mg
65	3/12	Major abdominal surgery	30/28	0.0125 mg/kg/ bolus	PCA morphine/ ketamine or PCA morphine; PCA morphine consumption 0–24 h post-op.	VRS at 15, 30, 60, 120 min, and 6, 12, 24 h after surgery	24 h median morphine consumption reduced from 49 to 46.5 mg $P < 0.001$	Pain scores lower at 15,30 and 60 min $P < 0.001$	Post-op. loading dose of morphine 0.05 mg/kg when VRS ≥ 2

Only data from the first 24 post-operative hours included.

Table 9

Studies (treatment arms) with PCEA ketamine + morphine (and other drugs), compared with PCEA morphine (and other drugs)

Reference	Quality score/OPVS	Surgical procedure	*n*, ketamine/ placebo	PCEA ketamine	Treatment of residual pain; Assessment of need for rescue analgesics	Assessment of pain	Outcome: need for rescue analgesics	Outcome: pain score	Comment
34	4/12	Major intrathoracic or upper abdominal	45/46	Basal infusion: 1 mg/ h, titrated Bolus: 1 mg	If VAS <3, basal infusion and bolus increased by 0.5 mg each; Cumulative total analgesic consumption	VAS daily for 3 days	Mean 24 h cumulative analgesic volume reduced from 96.6 to 74 ml $P < 0.05$	Mean VAS at rest reduced from 3 to 2 $P < 0.05$ Mean VAS on coughing reduced from 6.2 to 5.0 $P < 0.05$	Multimodal PCEAregime: bupivacaine + epinephrine + morphine
63	2/8	Lower abdominal	30/30	Loading dose: 5 mg Basal infusion: 0.5 mg/h Bolus: 0.5 mg	PCEA morphine/ ketamine or PCEA morphine Total consumption of morphine	VAS at 30 min, 3,6,12,18,24 h consumption reduced from 8.6 to 6.2 mg $P < 0.05$	24 h mean morphine consumption reduced from 8.6 mg to 6.2 mg $P < 0.05$	VAS at rest reduced 0–3 h post-op. $P < 0.05$	

Only data from the first 24 postoperative hours included.

mean difference of −15.7 mg. This review, including studies performed in children and adults, is restricted to randomized comparisons of ketamine with inactive controls.

Ten trials with 11 treatment arms and 417 patients in the comparison provided extractable data on 24-h PCA morphine consumption. When these data were combined, ketamine was shown to be effective in reducing post-operative morphine requirements. This should be interpreted with caution, as the number of patients is small, and doses and time of administration differ widely between trials. Performing separate meta-analysis on data from the separate treatment arms was considered but decided against, as the data were heterogenous and the number of patients in each analysis would be very small. The meta-analysis gave a WMD of −15.98 mg. The clinical relevance of this dose reduction in the first 24 h after surgery may be debated. When individual trial data were examined, including trials that were not included in the quantitative analysis, ketamine was generally reported to give a 30–50% reduction of rescue analgesics. A reduction of this order may well be clinically significant, especially in selected patient groups. Peri-operative ketamine may be useful for patients who traditionally require larger doses of opioids, such as cancer patients on long-term opioid therapy or the drug-dependent patient population. Patients who are especially sensitive to the adverse effects of opioids, such as the elderly, may also be a target group for this treatment. Randomized, placebo controlled trials in these patient groups would be clinically relevant.

Elia et al. (67) found that ketamine treatment did not reduce morphine-related adverse effects. They also found that the highest risk of hallucinations was in awake or sedated patients receiving ketamine without benzodiazepine, and that in patients undergoing general anaesthesia, the risk of hallucinations was low and independent of benzodiazepine premedication. In our own review where surgery was performed under general anesthesia in 35 out of the 37 included trials, ketamine-related adverse effects were mild or absent. Elia et al. analysing data from 391 patients treated with ketamine and 284 patients receiving inactive control, found no decrease in PONV. In contrast, our analysis of data from 705 patients treated with ketamine and 578 patients receiving active or inactive control, showed a significant reduction of nausea and vomiting in ketamine-treated patients.

Issues of optimal dose and form of administration are not resolved by the current data. The most common route of administration for ketamine was

Fig. 1. Meta-analysis: 24 h morphine consumption. PCA, patient-controlled analgesia; WMD, weighted mean difference; CI, confidence interval.

intravenous bolus and/or infusion, while 10 studies investigated epidural ketamine. Spinal ketamine is not a recommended route of administration due to unclear toxicity issues (1). Whether the isomers S(+) or R(–) ketamine have advantages over the racemate is not clear from the current data.

Three studies (41, 50, 53) were considered to be non-sensitive. The issue of study sensitivity in trial design is important. In general, sensitivity measures cannot be used for studies with PCA analgesic consumption as an endpoint (68). However, there are a number of factors which may decrease study sensitivity and which should be considered when designing clinical trials on post-operative pain. In one trial, all patients received a constant infusion of bupivacaine post-operatively (41), while in another, all patients received pre-treatment with ketorolac and pre-incisional skin infiltration with bupivacaine (50). These factors may have been responsible for low levels of pain. These studies could produce false/negative results as they would be unable to detect a difference between ketamine and placebo had there been one.

Only one study (36) included long-term follow-up regarding mechanical hyperalgesia and residual pain. An important question, which has not been addressed in the current literature, is whether ketamine prevents the development of hyperalgesia during surgery and/or the development of chronic post-surgical pain. NMDA receptor antagonists, including ketamine, have been shown to prevent the development of hyperalgesia (69, 70). Chronic post-surgical pain is more common than previously thought (71–74). Certain types of surgical intervention, for example thoracotomy and mastectomy, have a relatively high prevalence of chronic post-surgical pain. Studies with long-term follow-up in these patient groups would therefore be of interest.

Ketamine is a readily available, inexpensive drug. It is generally thought that it has limited usefulness in pain management due to adverse effects. This is not supported by the current evidence in relation to acute post-operative pain in adults where adverse effects were mild or absent. In fact, ketamine reduces post-operative nausea and vomiting. Because both ketamine and morphine are reported to cause nausea and vomiting, it is interesting that a combination of morphine and ketamine appears to reduce PONV. When low-dose ketamine is given to healthy volunteers, the incidence of nausea and vomiting appears to be greater than that reported in the clinical setting (1). The observed reduction in PONV in the studies included in this review may be due to a morphine-sparing effect or to other as yet undetermined factors. Not all trials provided

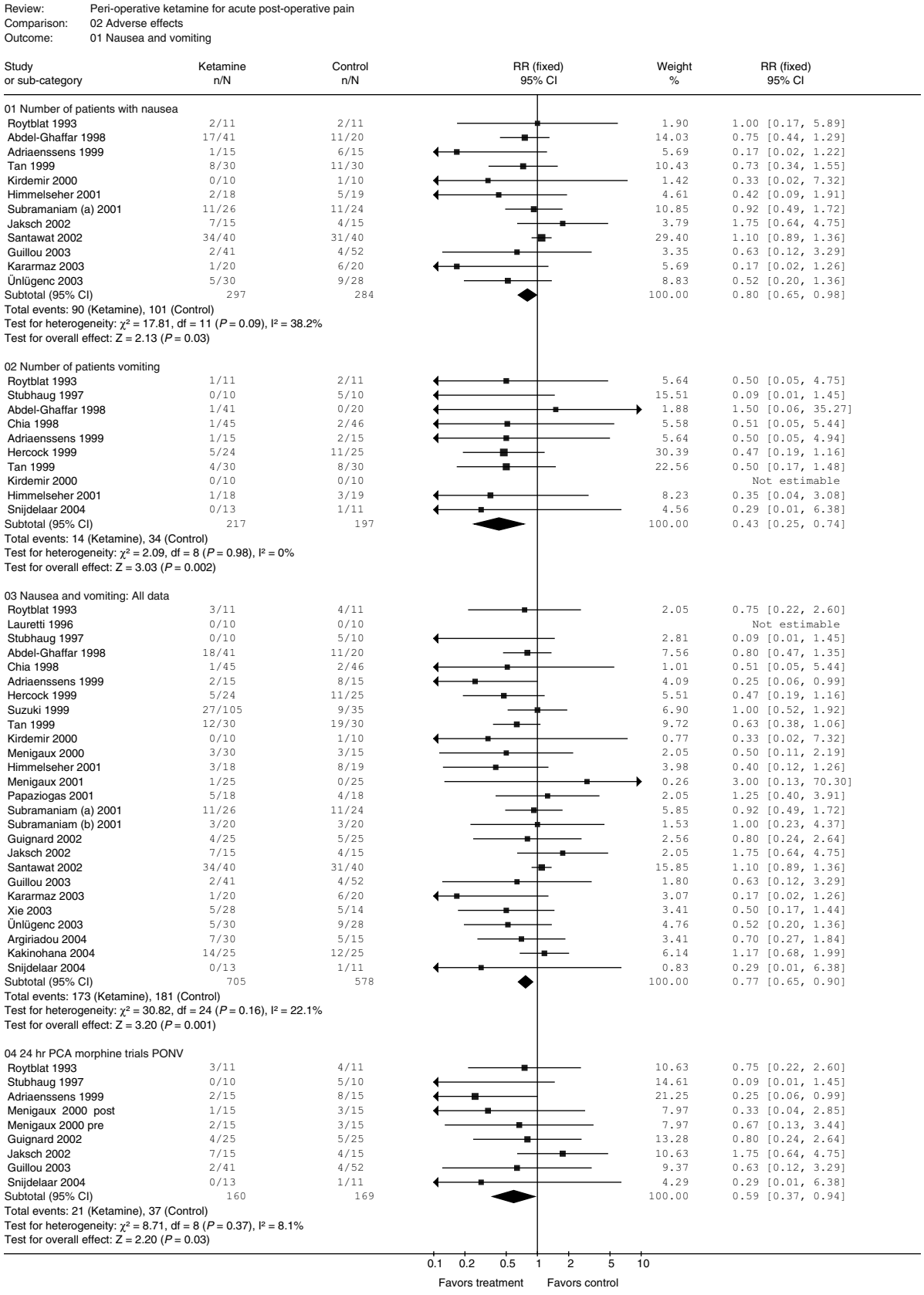

Fig. 2. Meta-analysis: adverse effects (nausea and/or vomiting). PONV, postoperative nausea and vomiting; WMD, weighted mean difference; RR, relative risk; CI, confidence interval.

extractable data regarding nausea and vomiting. It is recommended that future trials report adverse effects as dichotomous data.

The large number of papers retrieved shows that there is considerable interest in the use of ketamine for acute post-operative pain. A number of studies are only published as abstracts. It will be interesting to see whether they are ultimately published, and how the new data will contribute to current findings.

Conclusions

Ketamine is effective in reducing morphine requirements in the first 24 h after surgery. Adverse effects are mild or absent. Ketamine reduces post-operative nausea and vomiting. These data should be interpreted with caution as the retrieved studies were heterogenous and the result of the meta-analysis can not be translated into any specific administration regimen with ketamine.

Future trials should focus on optimal dose and have long-term follow-up with regard to the development of hyperalgesia and chronic post-surgical pain. Trials of peri-operative ketamine in selected patient groups where opioid sparing is desirable would be of interest. Better reporting of adverse effects, for example as dichotomous data, is required.

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