Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review

Kathirvel Subramaniam, MD, Balachundhar Subramaniam, MD, and Richard A. Steinbrook, MD

From the Department of Anesthesiology, Critical Care & Pain Management, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Animal studies on ketamine and opioid tolerance have shown promising results. Clinical trials have been contradictory. We performed a systematic review of randomized, double-blind clinical trials of ketamine added to opioid analgesia. Thirty-seven trials with 51 treatment arms and 2385 patients were included. Studies were divided into 5 subgroups: IV ketamine as single dose ($n = 11$), continuous infusion ($n = 11$), patient-controlled analgesia (PCA) ($n = 6$), epidural ketamine with opioids ($n = 8$), and studies in children ($n = 4$). Outcome measures included pain scores, time to first request for analgesia, supplemental analgesics, and adverse events. Efficacy was estimated by statistical significance ($P < 0.05$) of outcome measures as reported in studies and also by calculation of weighted mean difference for pain scores during the first 24 h after surgery. As compared to morphine alone, IV PCA with ketamine and morphine did not improve analgesia. Intravenous infusion of ketamine decreased IV and epidural opioid requirements in 6 of 11 studies. A single bolus dose of ketamine decreased opioid requirements in 7 of 11 studies. Five of 8 trials with epidural ketamine showed beneficial effects. Adverse effects were not increased with small dose ketamine. We conclude that small dose ketamine is a safe and useful adjuvant to standard practice opioid-analgesia.

(Anesth Analg 2004;99:482–95)

Ketamine is an IV anesthetic with analgesic properties in subanesthetic doses (1–5). Interest in the analgesic properties of small-dose ketamine has prompted clinical trials comparing opioids and ketamine. The results of these trials have shown that analgesia produced by ketamine alone was not equivalent to that produced by opioid analgesics (6–9). However, recognition of its actions on *N*-methyl-D-aspartate (NMDA) receptors renewed clinical interest in ketamine as a perioperative analgesic. Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal root neurons. This induces central sensitization, wind-up phenomenon, and pain memory. Ketamine, a noncompetitive antagonist of NMDA receptors, can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon (10). It has also been reported that μ receptor activation by opioids leads to a sustained increase in glutamate synaptic effectiveness at the level of NMDA receptors. Opioids when used alone in large doses for a prolonged period induce tolerance, which may lead to increased postoperative pain (11). Ketamine, by blocking these NMDA receptors, can prevent the development of tolerance. This has been studied extensively in animals and consistently produced positive results (12–15). This concept was the basis for multiple clinical trials involving ketamine as an adjuvant to opioids and multimodal analgesia. Contrary to the experimental evidence, clinical trials in humans have shown mixed results. We performed a qualitative and quantitative systematic review of randomized, double-blind clinical trials of ketamine added to opioid analgesia to provide a reasonable answer to this controversy.

Methods

Reports of randomized double-blind clinical trials of ketamine added to opioid analgesia for postoperative pain relief were sought systematically using the Cochrane Library 2003 (www.cochrane.org) and MEDLINE (1966–2003) (www.ncbi.nlm.nih.gov/pubmed)

Accepted for publication January 7, 2004.

Address correspondence and reprint requests to Kathirvel Subramaniam, MD, Department of Anesthesiology, Critical Care & Pain Management, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston MA 02215. Address email to kathirvels@yahoo.com.

DOI: 10.1213/01.ANE.0000118109.12855.07

0003-2999/04

databases without language restriction. Abstracts, letters of correspondence, and unpublished observations were not considered for the review.

The following search terms were used: ketamine, morphine, fentanyl, alfentanil, sufentanil, remifentanil, ketamine with morphine, ketamine with opioid, ketamine and morphine, postoperative analgesia, postoperative pain relief, postoperative pain, opioid tolerance, and multimodal analgesia. Lists of references of individual articles and review articles were also searched for additional relevant articles. Authors were contacted for the missing information on methods such as randomization and blinding or for original data such as pain scores if necessary.

Two authors read all selected articles independently and consensus was subsequently achieved. Studies were considered for this review if they compared two groups, one group with opioid analgesia and another group with ketamine added to opioid analgesia. Type of opioid administered was noted but studies involving all opioids (meperidine, morphine, fentanyl, alfentanil, sufentanil, and remifentanil) were considered. Route (IV, IM, subcutaneous [SC], and epidural) and dose of opioid should have been similar in both groups. Route (IV, IM, SC, and epidural), method (single bolus, infusion, and patient-controlled analgesia [PCA]), and timing of administration of opioid and ketamine (postoperative, preoperative) were noted.

Studies comparing preincisional versus postincisional administration of ketamine alone (16–18) or in combination with opioids (19–22) were excluded. Studies comparing "opioids" with "ketamine as a sole analgesic" were not considered. Studies involving another class of analgesics along with opioids and ketamine, if common to both groups (local anesthetics, nonsteroidal antiinflammatory drugs [NSAIDs], clonidine, and neostigmine) were noted but not excluded.

Each report that met the inclusion criteria was scored using a 3 item, 1–5 score quality scale (23). If the study was described as randomized, one point was given and an additional point was given if the method of randomization was described and considered adequate (e.g., computer-generated, table of random numbers). For trials described as double-blind, one point was given. An additional point was given if the method of blinding was described and considered adequate. Finally, reports that described the numbers and reasons for withdrawal were given one point. By definition, studies without randomization and blinding were excluded. Thus, the minimum score of an included trial was 2 and maximum score was 5. Trials with sample size <10 were not considered (24).

The following data were obtained from all included studies: number of patients, grouping of patients, ASA physical status, power calculation for sample size, type of surgery, intraoperative analgesics used, route (IV, epidural, intrathecal, and oral), dose and method (bolus, infusion, or PCA device) of administration of opioid and ketamine, other analgesics used, and duration of observation.

The postoperative analgesia outcome measures (pain scores, time to first requirement for analgesia (TFA) and total supplemental analgesic requirement (TSD)) for the first 24 h were noted for analysis.

The following adverse effects were noted for analysis: postoperative nausea and vomiting (PONV), sedation, respiratory depression, pruritus, and central nervous system (CNS) side effects (dizziness, disorientation, dysphoria, confusion, excessive sedation, bad dreams, strange feelings, and hallucinations).

Trials were stratified according to the route (epidural, IV) and method (infusion, bolus) of ketamine administration. Studies on pediatric patients were considered separately. Visual analog score (VAS, 0–100 mm, 0 = no pain and 100 = maximum pain), as pain outcome measure, was quantitatively analyzed. Verbal rating pain score (VRS, 0–100 mm), numeric rating score, and similar scores were converted to VAS pain scores (e.g., a 4-point VRS including no, mild, moderate, and severe pain was converted to 0, 25, 50, and 75 mm VAS respectively) for analysis. Mean VAS for each treatment group was determined for each trial from all available observations within 24 h after surgery. Quantitative analysis of combined VAS data from different studies over 24 h was performed using Review Manger 4.2. (Review Manager, Version 4.2; the Cochrane collaboration, The Nordic Cochrane center, Copenhagen, Denmark). Weighted mean difference (WMD) for VAS between the two treatment groups was calculated for each study and combined data. The weight given to each study was determined by the sample size and standard deviation of VAS scores in individual trials.

Qualitative evaluation of postoperative analgesic efficacy was done using significant differences ($P < 0.05$ as reported in the original articles) in pain scores, TFA, and TSD between the two groups.

Adverse effects such as CNS side effects, PONV, pruritus, and respiratory depression were quantitatively analyzed after summation of events from all studies. Relative risk (RR) was considered statistically significant when the 95% confidence interval (CI) did not include 1.

Results

Thirty-seven trials with 51 treatment arms were included for analysis (Tables 1–6). A total of 2385 patients were studied, of whom 1336 received ketamine. Intravenous ketamine was administered as a bolus in 11, as an infusion in 11, and as IV PCA in 6 clinical trials. Epidural ketamine was studied as an adjuvant

Table 1. Intravenous Patient-Controlled Analgesia With Ketamine and Morphine

Clinical trial	Quality Score	Number of patients (C/K)	Morphine: Ketamine in IV PCA (mg/mL)	Surgery	Pain scores	PCA Morphine Used	Side Effects
Reeves et al. 2001 (28)	5	35/36	1:1	Major Upper abdominal	NS	NS	Relative risk for vivid dreams 1.8 in ketamine group
Hercock et al. 1999 (29)	4	25/24	1:1	Lower abdominal Hysterectomy	NS	NS	Less sleepiness and fewer antiemetics in ketamine group ($P < 0.05$)
Murdoch et al. 2002 (30)	4	19/21	1:0.75	Lower abdominal Hysterectomy	NS	NS	Pruritus less in ketamine group ($P < 0.05$)
Burstal et al. 2001 (31)	5	33/37	1:2	Lower abdominal Hysterectomy	NS	NS	More side effects in ketamine group ($P < 0.05$)
Unlugenc et al. 2003 (32)	4	28/30	0.4:1	Major abdominal surgery	$P < 0.001$ at 15 and 30 min	NS	NS
Javery et al. 1996 (33)	3	20/22	1:1	Lumbar Microdiscectomy	$P < 0.001$	$P < 0.001$	Less nausea, pruritus, urinary retention in ketamine group, $P < 0.05$

C = control (opioids only group); K = ketamine group; IV PCA = intravenous patient-controlled analgesia; NS = no significant difference between the groups; *P* values indicate beneficial effects for ketamine group unless otherwise indicated.

Table 2. Intravenous Ketamine as Continuous Infusion with Intravenous Opioids

Clinical trial	Quality Score	Number of patients (C/K)	Dose of Ketamine	Timing of ketamine administration	Type of Surgery	Pain Scores	TFA	TSD	Side Effects
Edwards et al. 1993 (34)	3	10/30, three treatment arms	5, 10, 20 mg/h	Intraop & 24 h Postop	Upper abdominal	NS	–	NS	$P < 0.05$ for dreams more in ketamine groups
Stubhaug et al. 1997 (35)	4	10/10	0.12 mg/kg/h	Preop Intraop & 48 h Postop	Donor Nephrectomy	$P < 0.05$ in First hour postop	$P < 0.05$	$P < 0.05$ first 4 h postop	$P < 0.05$ for PONV
Adriaenssens et al. 1999 (36)	3	15/15	0.15 mg/kg/h	Postop 48 h	Major abdominal	$P < 0.05$ in First hour postop	–	$P < 0.05$	$P < 0.05$ for nausea
Jaksch et al. 2002 (37)	5	15/15	0.12 mg/kg/h	Preop & Intraop & 2 h Postop	Knee Arthroscopy	NS	NS	NS	NS
Guignard et al. 2002 (38)	5	25/25	0.12 mg/kg/h	Preop & Intraop	Open colorectal	$P < 0.05$ in first 15 min	$P < 0.01$	$P < 0.01$	NS
Heinke and Grimm 1999 (39)	2	13/13	0.6 mg/kg/h	Preop & Intraop	Gynecologic laparotomy	$P = 0.05$ for day 2	$P < 0.01$	NS	NS
Guillou et al. 2003 (40)	4	52/41	0.12 mg/kg/h	Postop 48 h	Major abdominal surgery	$P < 0.05$ at 16, 20, 40, 44 h	–	$P < 0.05$	NS

C = control (opioids only group); K = ketamine group; PCA = patient-controlled analgesia; TFA = time to first request for analgesia; TSD = total supplemental analgesic requirement; PONV = postoperative nausea and vomiting; Preop = before surgery; Intraop = during surgery; Postop = after surgery; NS = no significant difference between the groups.
P values indicate beneficial effects for ketamine group unless otherwise indicated.

to epidural opioids in 8 trials. Twenty trials reported improvement in analgesia with the addition of ketamine to opioids whereas 17 trials did not find significant clinical benefit. Average quality score was 4.1 for both negative and positive clinical trials. No significant correlation was detected between the timing of ketamine administration and its analgesic efficacy. Ketamine was given before incision in 52% of the

Table 3. Intravenous Ketamine as Continuous Infusion with Epidural Opioids

Clinical trial	Quality Score	Number of patients (C/K)	Dose/timing of Ketamine	Opioids Used	Surgery	Pain scores	TSD	Side Effects
De Kock et al. 2001 (41)	5	20/40, two treatment arms	0.125 Gp1 & 0.25 Gp2 mg/kg/h Preop & intraop	Sufentanil	Rectal surgery	NS	NS	NS
Aida et al. 2000 (42)	4	30/31	0.5 mg/kg/h Preop & intraop	Morphine	Gastrectomy	$P < 0.05$	$P < 0.05$	–
Ilkjaer et al. 1998 (43)	4	28/24	10 mg/h Preop, Intraop & postop	Morphine	Nephrectomy	NS	NS	Increased Sedation with ketamine
Kararmaz et al. 2003 (44)	4	20/20	0.5 mg/kg/h Preop & Intraop	Morphine	Renal surgery	$P < 0.01$	$P < 0.01$	$P < 0.05$ for nausea and pruritus

C = control (opioids only group); K = ketamine group; TSD = total supplemental analgesic requirement; NS = no significant difference between the groups; Preop = before surgery; Intraop = during surgery; Postop = after surgery; Gp 1 = Group 1; Gp 2 = Group 2.
P values indicate beneficial effects for ketamine group unless otherwise indicated.

positive studies and in 60% of negative studies. Three studies were not suitable for analysis and were excluded: in one study, the number of patients was <10 (25), in another, patients in both groups received ketamine in the perioperative period (26), and in a third study, the patients were not randomized (27).

Quantitative analysis was performed on mean VAS pain scores recorded within 24 h after surgery and for adverse events (PONV, CNS side effects, pruritus, and respiratory depression) for ketamine treatment and controls. Data on analgesic consumption, TFA allowed a qualitative analysis because of the variety of analgesics, doses, and outcome reporting were used. Statistical difference between ketamine treatment and control regarding these measures was extracted from original reports and documented (Tables 1–6).

Six trials (28–33) compared IV PCA using the combination of morphine and ketamine with morphine alone (Table 1). These involved 330 patients, of whom 170 received ketamine with morphine IV PCA. Five trials noted no significant improvement in analgesia, with no significant differences in pain scores or total morphine consumption between the groups (28–32). Only one trial (33) in lumbar microdiscectomy showed a clear advantage for adding ketamine with reduction of pain scores, analgesic supplements, and adverse effects of opioids. The quality score of this positive study was 3; whereas the average quality score for negatively reported trials was 4.4.

Mean resting VAS for the first 24 h was analyzed with available data from 5 studies. Test for heterogeneity was significant, giving a random effects model. Overall WMD of −5.4 mm (95% CI, −1.26, 0.18) for VAS at rest was statistically not significant between the groups (Fig. 1). Three trials had VAS scores <2 (29,31,32). Two negative clinical trials mentioned power calculation based on VAS scores. VAS during movement was mentioned in 3 trials (28,29,31). A WMD for VAS of −2.7 mm (95% CI, −0.98, 0.44) was not significant.

Adverse effects (dreams, disorientation, dysphoria, and psychomimetic effects) were increased in ketamine-treated patients in two studies. Reeves et al. (28) reported RR for vivid dreams and hallucinations of 1.8 and 1.3, respectively, in ketamine-treated patients. Burstal et al. (31) noted discontinuing PCA in 4 of 37 patients who received ketamine because of dysphoria. However, CNS side effects analyzed for pooled data from all studies did not reveal any significant differences (27 of 146 (18%) in ketamine plus morphine versus 20 of 135 (15%) in morphine PCA groups ($P = 0.31$; RR, 1.27; 95% CI, 0.80, 2.01) (Table 7). PONV was reduced with ketamine in two studies (29,33). Pruritus was significantly less in patients treated with ketamine in two studies (30,33). Respiratory depression was noted in 2 patients of Reeves et al. (28). One of them received ketamine. In one study, ketamine-treated patients were less sleepy (29) whereas other studies did not show any significant effect of ketamine on sedation.

Overall, adding ketamine to morphine in IV PCA is not beneficial in improving the quality of postoperative analgesia, although side effects were not increased by the addition of ketamine.

Seven trials with nine treatment arms were identified using ketamine as a continuous infusion, in addition to IV opioids, in the perioperative period (34–40) (Table 2). Two-hundred-eighty-nine patients were studied; 149 patients received ketamine infusion. Four studies (35,36,38,40) reported significantly improved analgesia with an average quality score of 4. Three studies (34,37,39) reported no difference with an average quality score of 3.3.

Table 4. Intravenous Ketamine Given as Single Bolus with Intravenous Opioids

Clinical trial	Quality Score	Number of patients (C/K)	Ketamine Dose/timing	Opioids Used	Type of surgery	Pain scores	TFA	TSD	Side Effects
Suzuki et al. 1999 (45)	5	35/105 three treatment arms	0.05, 0.075 & 0.1 mg/kg Postop	Morphine	Ambulatory surgery	$P < 0.0001$ for 0.075 & 0.1 mg/kg	–	$P < 0.05$	NS
Menigaux et al. 2001 (46)	5	25/25	0.15 mg/kg Preop	Alfentanil	Arthroscopic Menisectomy	$P < 0.05$	–	$P < 0.05$	NS
Menigaux et al. 2000 (47)	5	15/30 two treatment arms	0.15 mg/kg Preop-Gp1, Postop-Gp2	Sufentanil	Anterior cruciate ligament repair	NS	$P < 0.05$	$P < 0.05$	NS
Roytblat et al. 1993 (48)	3	11/11	0.15 mg/kg Preop	Fentanyl	Open Cholecystectomy	$P < 0.05$ in First 5 h	$P < 0.05$	$P < 0.05$	NS
Dahl et al. 2000 (49)	4	29/33 (pre) & 27 (post) two treatment arms	0.4 mg/kg Preop-Gp1, Postop-Gp2	Alfentanil	Abdominal Hysterectomy	$P < 0.05$ in First 6 h (Gp2)	–	–	NS
Weinbroum 2003 (50)	4	114/131	0.25–0.75 mg/kg postop	Fentanyl intraop/ Morphine Postop	Abdominal, Transthoracic lung biopsy, Orthopedic	$P < 0.001$	NA	$P < 0.001$	Less PONV & more central side effects in ketamine
Kudoh et al. 2002 (51)	3	35/35	1 mg/kg preop	Fentanyl	Orthopedic	$P < 0.05$ at 8 and 16 h	–	–	NS
Mathisen et al. 1999 (52)	4	20/40 two treatment arms	1 mg/kg Preop-Gp1, Postop-Gp2	Alfentanil, Fentanyl	Laparoscopic Cholecystectomy	$P < 0.05$ at 30 min Gp2	–	NS	NS
Heinke and Grimm 1999 (39)	2	13/13	0.5 mg/kg in Postop	Alfentanil	Gynecological laparotomy	$P = 0.05$ on day 2	$P < 0.05$	NS	NS
Lehmann and Klaschik 2001 (53)	4	40/40	0.15 mg/kg Preop	Fentanyl	Laparoscopic or proctological surgery	NS	NS	NS	NS
Xie et al. 2003 (54)	5	14/14	0.5 mg/kg Preop	Fentanyl	Selective Gastrectomy	$P < 0.05$	$P < 0.05$	$P < 0.05$	NS

C = control (opioids only group); K = ketamine group; TFA = time to first request for analgesia; TSD = total supplemental analgesic requirement; NS = no significant difference between the groups, Preop = before surgery; Intraop = during surgery; Postop = after surgery; Gp1 = Group 1; Gp2 = Group 2; PONV = postoperative nausea and vomiting.
P values indicate beneficial effects for ketamine group unless otherwise indicated.

In a dose response study, Edwards et al. (34) did not find a significant decrease in pain scores or analgesic consumption with 5, 10, or 20 mg/h ketamine infusions although adverse events such as dreaming increased with increasing infusion rate.

Stubhaug et al. (35) reported short lasting benefit of ketamine in the early postoperative period (decreased VAS for 1 h, longer TFA, and decreased morphine consumption for 4 h). The main conclusion of their study was that areas of punctuate hyperalgesia and numbers of patients with wind-up pain were significantly reduced by ketamine infusion. There was no correlation with the degree of pain or morphine consumption.

Quantitative analysis of mean VAS at rest for 24 h was performed with available data from 6 studies and 8 treatment arms. One study did not report actual VAS scores (38). In another trial (34), 5-point VRS (no pain, mild, moderate, severe, very severe) was converted to VAS of 0, 25, 50, 75, and 100 mm respectively. A random effects model was used because the test for heterogeneity was significant. WMD for VAS was −8.2 mm (95% CI, −1.51, −0.14) with beneficial effect for the ketamine infusion groups (Fig. 2). Two studies had VAS less than 3 in both groups (37,40). VAS with movement was reported in two trials, with no significant differences between the groups (39,40). Power analysis for reduction of morphine consumption was performed in 5 of 7 trials.

CNS side effects (diplopia, dreams, dizziness, dysphoria) were not significantly increased ($P = 0.09$) with IV ketamine infusion (15 of 149 (10%) in

Table 5. Epidural Ketamine with Epidural Opioids

Clinical trial	Quality score	Numbers (C/K)	Dose & timing of Ketamine	Opioids Used	Type of surgery	Pain scores	TFA	TSD	Side effects
Tan et al. 1999 (55)	3	30/30	PCEA basal rate 1 mL/h (0.5 mg/mL)	Morphine	Lower abdominal hysterectomy/colectomy)	$P < 0.05$ First 3 h	–	$P < 0.05$	NS
Chia et al. 1998 (56)	4	46/45	PCEA basal rate 2.5 mL/h (0.4 mg/mL)	Morphine	Upper abdominal	$P < 0.05$	–	$P < 0.05$	NS
De Kock et al. 2001 (41)	5	20/40 two treatment arms	Intraop infusion 0.125 & 0.25 mg/kg/h	Sufentanil	Rectal surgery	NS	–	NS	NS
Subramaniam et al. 2001 (57)	4	24/26	Preop bolus 1 mg/kg	Morphine	Upper abdominal	–	$P < 0.05$	NS	NS
Subramaniam et al. 2001 (58)	4	20/20	Postop bolus 1 mg/kg	Morphine	Upper abdominal	–	$P < 0.05$	$P < 0.05$	Increased Sedation in ketamine
Taura et al. 2003 (59)	5	50/54	Postop bolus 20/30 mg	Morphine	Hepatectomy	$P < 0.05$	$P < 0.05$	$P < 0.05$	NS
Santawat et al. 2002 (60)	4	40/40, two treatment arms	30 mg Preop & postop bolus groups	Morphine	Gynecology	NS	NS	NS	NS
Xie et al. 2003 (54)	5	14/14	0.5 mg/kg Preop bolus	Fentanyl, PCEA morphine	Selective Gastrectomy	$P < 0.05$	$P < 0.05$	$P < 0.05$	NS

C = control (opioids only group); K = ketamine group; PCEA = patient-controlled epidural analgesia; TFA = time to first request for analgesia; TSD = total supplemental analgesic requirement; NS = no significant difference between the groups; Preop = before surgery; Intraop = during surgery; Postop = after surgery.

P values indicate beneficial effects for ketamine group unless otherwise indicated.

Table 6. Ketamine as Adjuvant to Opioids in Children

Clinical trial	Quality score	Number (C/K)	Dose & timing of Ketamine	Opioids Used	Type of surgery	Pain scores	TFA	TSD	Side effects
Ozbek et al. 2002 (61)	4	35/36	0.5 mg/kg Preop bolus caudal	Alfentanil	Hypospadias Repair	NS	$P = 0.001$	$P < 0.001$	NS
Elhakim et al. 2003 (62)	5	25/25	0.1 mg/kg Preop IM	Fentanyl	Tonsillectomy	$P < 0.05$	$P < 0.01$	$P < 0.05$	NS
O'Flaherty and Lim 2003 (63)	4	20/18	0.15 mg/kg at Preop IV	Fentanyl	Tonsillectomy	NS	–	NS	NS
Dix et al. 2003 (64)	5	23/50, two treatment arms	Gp 1 = 0.5 mg/kg IV Preop Gp 2 = 0.5 mg/kg IV Preop & 4 μg/kg/min IV Postop	Fentanyl	Appendicectomy	NS	–	NS	More in Gp 2 ($P < 0.05$)

C = control (opioids only group); K = ketamine group; PCEA = patient-controlled epidural analgesia; TFA = time to first request for analgesia; TSD = total supplemental analgesic requirement; NS = no significant difference between the groups; Preop = before surgery; Postop = after surgery; IV = intravenous; IM = intramuscular; Gp 1 = Group 1; Gp 2 = group 2.

P values indicate beneficial effects for ketamine group unless otherwise indicated.

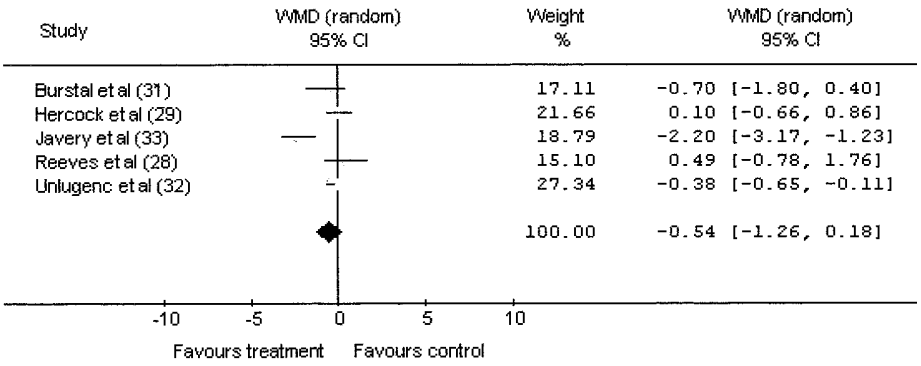

Figure 1. Intravenous patient-controlled analgesia with morphine in patient-controlled analgesia (visual analog scale at rest). WMD = weighted mean difference; CI = confidence interval).

Table 7. Incidence of Central Nervous System Side Effects

Study	Ketamine + opioid group	Opioid only group	RR (95% CI), fixed effects model
IV PCA ketamine with morphine			
Reeves et al. (28)	22/36	13/35	1.65 (0.99–2.72)
Murdoch et al. (30)	0/21	4/19	1.29 (0.80–2.01)
Burstal et al. (31)	4/37	0/33	8.05 (0.45–144.15)
Unlugenc et al. (32)	0/30	0/28	
Javery et al. (33)	1/22	3/20	0.30 (0.03–2.68)
Overall	27/146	20/135	1.27 (0.80–2.01)
IV ketamine continuous infusion			
Edwards et al. (34)	7/30	0/10	5.32 (0.33–85.70)
Stubhaug et al. (35)	1/10	2/10	0.50 (0.05–4.67)
Adriaenssens et al. (36)	3/15	3/15	1.00 (0.24–4.18)
Jaksch et al. (37)	1/15	1/15	1.00 (0.07–14.55)
Guignard et al. (38)	0/25	0/25	
Heinke and Grimm (39)	0/13	0/13	
Guillou et al. (40)	3/41	3/52	1.27 (0.27–5.96)
Overall	15/149	9/140	1.31 (0.57–3.00)
IV ketamine, Single bolus			
Suzuki et al. (45)	17/105	3/35	1.89 (0.59–6.06)
Menigaux et al. (46)	2/25	1/25	2.00 (0.19–20.67)
Menigaux et al. (47)	0/30	0/15	
Roytblat et al. (48)	0/11	0/11	
Weinbroum (50)	10/131	0/114	18.30 (1.08–308.79)
Kudoh et al. (51)	5/35	8/35	0.63 (0.23–1.72)
Mathisen et al. (52)	0/40	0/20	
Heinke and Grimm (39)	1/13	0/13	3.00 (0.13–67.51)
Lehmann et al. (53)	3/40	4/40	0.75 (0.18–3.14)
Xie et al. (54)	0/14	0/14	
Overall	38/444	16/322	1.61 (0.91–2.83)
Epidural ketamine (8 studies)	2/269	0/244	2.13 (0.22–21.15)

Values are number of patients with side effects/number of patients in the study.
RR = relative risk; CI = confidence interval; IV PCA = intravenous patient-controlled analgesia.

ketamine-treated patients versus 9 of 140 (6.4%) in patients treated with only opioids (RR, 1.31; 95% CI, 0.57, 3.00) (Table 7). Five of the 15 patients who experienced dreams received the most rapid infusion rate (20 mg/h) of ketamine in Edwards et al. 's study (34).

PONV data were available in 5 trials (Table 8). Combining the data from these studies, no significant differences were found between the groups, though there was a trend towards less PONV in ketamine-treated patients (15 of 106 [14%] versus 27 of 117 [23%] in patients who received opioids only; RR, 0.58; 95% CI, 0.33, 1.02; $P = 0.06$).

One patient in the ketamine group and two patients in the control group developed pruritus (37,40). Hypoventilation and respiratory depression were reported in 3 patients each in ketamine and control groups from 2 studies (34,40). Guignard et al. (38), found increased sedation for 15 min in the immediate postoperative period and Heinke and Grimm (39) reported longer time to orientation in ketamine group

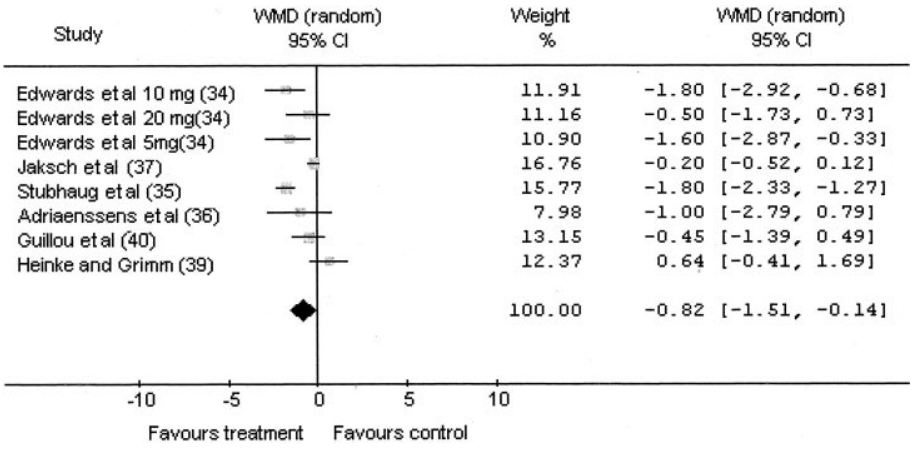

Figure 2. Intravenous ketamine infusion with intravenous opioids (visual analog scale at rest). WMD = weighted mean difference; CI = confidence interval).

Table 8. Incidence of Postoperative Nausea and Vomiting

Study	Ketamine + opioid group	Opioid only group	RR (95% CI)
IV ketamine continuous infusion			
Stubhaug et al. (35)	0/10	6/10	0.08 (0.00–1.21)
Adriaenssens et al. (36)	2/15	8/15	0.25 (0.06–0.99)
Jaksch et al. (37)	7/15	4/15	1.75 (0.64–4.75)
Guignard et al. (38)	4/25	5/25	0.80 (0.24–2.64)
Guillou et al. (40)	2/41	4/52	0.63 (0.12–3.29)
Overall	15/106	27/117	0.58 (0.33–1.02)
IV ketamine, Single bolus			
Suzuki et al. (45)	28/105	9/35	1.04 (0.54–1.98)
Menigaux et al. (47)	3/30	3/15	0.50 (0.11–2.19)
Roytblat et al. (48)	3/11	4/11	0.75 (0.22–2.60)
Weinbroum (50)	16/131	42/114	0.33 (0.20–0.56)
Lehmann et al. (53)	15/40	13/40	1.15 (0.63–2.10)
Xie et al. (54)	2/14	3/14	0.67 (0.13–3.40)
Overall	74/391	75/258	0.76 (0.44–1.32)
Epidural ketamine			
Tan et al. (55)	12/30	19/30	0.63 (0.38–1.06)
Chia et al. (56)	1/45	3/46	0.34 (0.04–3.15)
Subramaniam et al. (57)	11/26	11/24	0.92 (0.49–1.72)
Subramaniam et al. (58)	3/20	3/20	1.00 (0.23–4.37)
Taura et al. (59)	9/54	6/50	1.39 (0.53–3.62)
Santawat et al. pre* (60)	17/20	16/20	1.06 (0.80–1.41)
Santawat et al. post* (60)	17/20	15/20	1.13 (0.83–1.55)
Xie et al. (54)	0/14		
Overall	70/229	76/224	0.90 (0.73–1.12)

Values are number of patients with postoperative nausea and vomiting/number of patients in the study.
RR = relative risk; CI = confidence interval.
* Santawat et al. (60) had 2 treatment arms: preincisional and postincisional.
In calculating relative risk and 95% CI, the fixed effects model was used for the IV ketamine continuous infusion and epidural ketamine studies; the random effects model was used for the IV ketamine, single bolus studies.

patients whereas others did not find any significant increase in sedation with ketamine.

Intravenous ketamine infusion was given in combination with epidural opioids in 4 studies (41–44) with 5 treatment arms (Table 3). A total of 213 patients were studied; 115 received ketamine. Two studies noted significant reductions in VAS and postoperative opioid consumption (42,44). Wound hyperalgesia was studied in two studies (41,43); one reported decreased areas of hyperalgesia (41). The same study also reported decreased residual pain and decreased need for chronic medications at 2 wk, 1 and 6 mo, and 1 yr. Side effects were reported in three studies (41,43,44). CNS side effects (psychomimetic effects such as hallucinations, diplopia, dreams) were noted in 10.7% (9 of 84) of patients in the ketamine group and 4.4% (3 of 68) in control patients ($P = 0.25$). Kararmaz et al. (44) noted significant reduction in the incidence of nausea

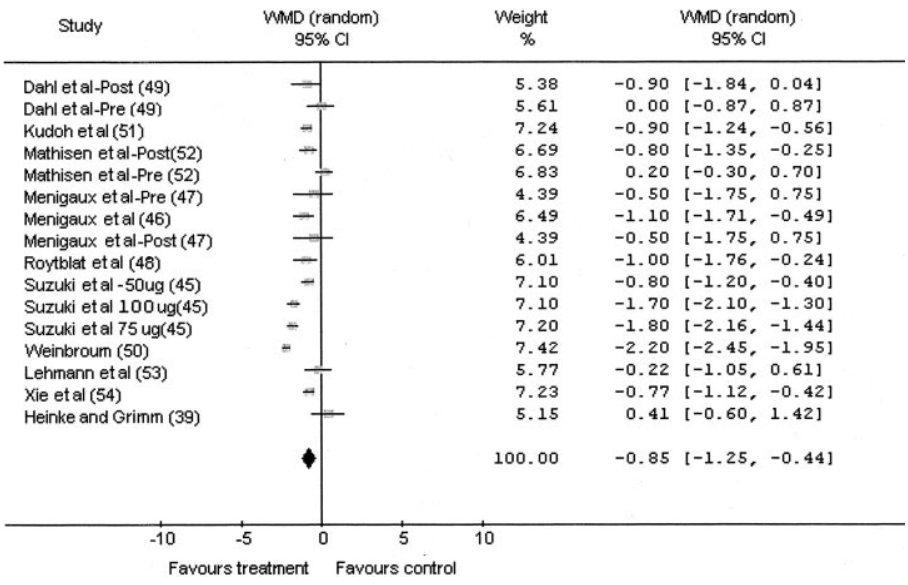

Figure 3. Intravenous ketamine single bolus with intravenous opioids (visual analog scale at rest). WMD = weighted mean difference; CI = confidence interval).

and itching with the addition of ketamine whereas others did not find any significant difference. Sedation was increased in two studies with ketamine infusion (43,44). In conclusion, of the 4 studies, 2 studies reported beneficial effects of ketamine in acute postoperative pain (42,44) whereas another reported decreased wound hyperalgesia and chronic residual pain (41). Ilkjaer et al. (43) administered epidural morphine in combination with IV ketamine only during the second 24 h after surgery when the intensity of pain had decreased, thus reducing the significance of their negative findings.

Overall, continuous IV ketamine infusion produced promising results in 6 of 11 clinical trials in improving perioperative opioid analgesia. The incidence of adverse effects was not increased by the addition of ketamine.

Ketamine was administered as a single IV bolus with IV opioids in 11 clinical trials (45–54) (Table 4). Sixteen treatment arms with 855 patients were found; 504 patients received ketamine. Seven trials with an average quality score of 4.3 reported a positive influence of adding ketamine on postoperative analgesia (45–48,50,51,54). Four clinical trials with an average quality score of 3.5 reported no significant effect of adding ketamine (39,49,52,53). Two positive trials (46,47) and one negative trial (52) mentioned power calculations. Three positive reports (46,48,54) and 2 negative reports (52,53) had mean VAS <3.

Of the 11 trials, 8 (45,46,48–52, 54) reported improved VAS scores at some time. Quantitative analysis of VAS at rest over 24 h was performed using a random effect model (test of heterogeneity was significant). The data from all clinical trials ($n = 11$) with 16 treatment arms were considered for analysis. WMD of −8.5 mm (CI 95%, −1.25, −0.44) was obtained in favor of ketamine coadministration (Fig. 3). VAS with movement was mentioned in 4 treatment arms in 3 trials. Fixed effects model was used as P value for heterogeneity = 0.32. WMD of −6.2 mm (95% CI, −0.83, −0.41) was obtained in favor of ketamine groups.

Suzuki et al. (45) in a dose response study, used 3 doses of ketamine (50, 75, and 100 μg/kg), in addition to morphine, for outpatient surgery. Patients were followed through phase 2 recovery. They concluded that ketamine doses of 75 and 100 μg/kg significantly decreased VAS and supplemental analgesic administration in the postanesthesia care unit.

TFA was reported in 5 clinical trials and was significantly prolonged with ketamine in 4 trials. TSD were reported in 9 trials and were significantly decreased in 6.

Nine percent (38 of 444) of ketamine patients experienced CNS side effects (strange sensation, lightheadedness, dreams, sleep difficulties, and confusion) compared with 5% (16 of 322) of control group patients; this difference was not statistically significant, ($P = 0.10$; RR, 1.61; 95% CI, 0.91, 2.83) (Table 7).

Analysis of combined data on the incidence of PONV revealed that there was a trend towards less PONV in ketamine-treated patients compared with patients who received opioids alone (74 of 416 [18%] versus 75 of 283 [27%] control patients, $P = 0.33$; RR, 0.76; 95% CI, 0.44, 1.32). Test for heterogeneity was significant ($P = 0.02$) giving a random effects model (Table 8).

None of the patients in either group developed respiratory depression or pruritus. Two studies (39,52) found increased time to eye opening and orientation and one study (50) found increased wakefulness with ketamine. Other trials did not find any significant difference in sedation between the groups.

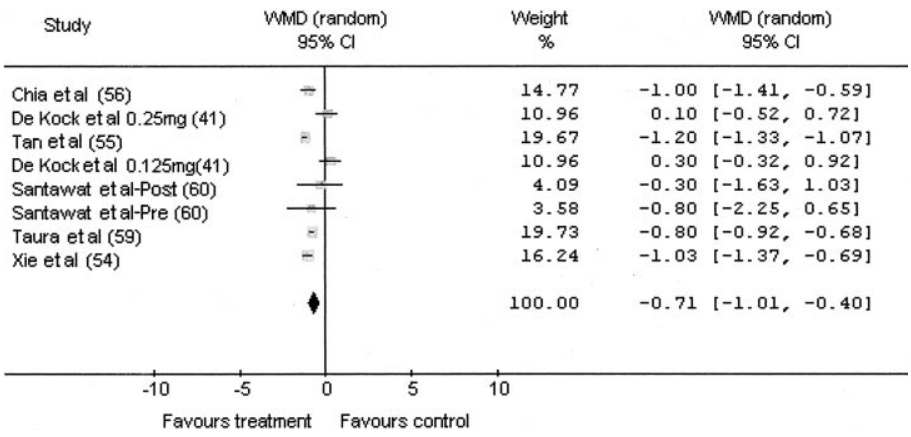

Figure 4. Epidural ketamine with epidural opioids (visual analog scale at rest). WMD = weighted mean difference; CI = confidence interval).

Overall, a single dose of IV ketamine improved postoperative analgesia with opioids. Side effects were not increased by a single bolus IV ketamine.

There were 8 clinical trials (41,54–60) with 10 treatment arms involving epidural ketamine (Table 5). Major intrathoracic and abdominal surgeries were chosen in all 8 trials. A total of 513 patients were studied; 269 patients received ketamine. Five studies reported a positive outcome with ketamine (54–56,58,59). The average quality score of positive trials was 4.2. One study reported a statistically significant prolongation in TFA but concluded that this was of no clinical relevance (57). Two studies reported no improvement of analgesia with the addition of ketamine (41,60). The average quality score of the negative trials was 4.3. Preincisional and postincisional epidural ketamine were administered in 2 studies, each as a single bolus, as an adjuvant to epidural morphine (54,57–59). Santawat et al. (60) studied the analgesic efficacy of adding epidural ketamine with both preincisional and postincisional morphine (2 treatment arms). Patient-controlled epidural analgesia (PCEA) with morphine and ketamine was studied in two clinical trials (55,56). De Kock et al. (41), studied ketamine as part of a balanced multimodal analgesic regimen (epidural sufentanil, bupivacaine, epinephrine, and clonidine with IV alfentanil as a rescue analgesic). Ketamine was administered epidurally as a bolus followed by continuous infusion in two different doses (2 treatment arms) in their study.

Sample size justification was stated in only 2 trials. Six trials reported VAS scores; 4 noted significant decreases in VAS with the addition of ketamine (54–56,59). Four studies noted significant increases in TFA with the addition of ketamine. Supplemental analgesic requirements were reported in all 8 clinical trials; 5 found significant reductions in analgesic requirements.

Quantitative analysis of VAS at rest and with coughing was performed with available data from 7 treatment arms. Because the test for heterogeneity was significant, a random effect model was used. WMD of −7.1 mm (95% CI, −1.01, −0.40) for mean VAS at rest in favor of ketamine group was obtained (Fig. 4). Five treatment arms had VAS less than 3 (42,54,55,59). WMD for VAS with movement was not significant between the groups (Fig. 5).

Psychomimetic effects were seen in 2 of 269 patients treated with ketamine compared with none of 244 patients who did not receive epidural ketamine (Table 7).

The incidence of PONV was similar in both groups (70 of 229 [31%] with ketamine versus 76 of 224 [34%] in the control group, $P = 0.36$; RR, 0.90; 95% CI, 0.73, 1.12) (Table 8).

Four studies with five treatment arms reported pruritus. The incidence of pruritus from pooled data was 40.5% (47 of 116) in patients who received ketamine with opioid and 45.6% (52 of 114) of the opioid only group patients ($P = 0.51$). One patient in Santawat et al. 's study (60) developed respiratory depression in the morphine plus ketamine preincisional group. One clinical trial (58) noticed increased sedation in ketamine group patients whereas others did not find any significant difference in sedation between the groups

In conclusion, epidural ketamine added to various opioid-based perioperative epidural analgesic regimens improved analgesia in 5 of 8 clinical trials with no increase in PONV or ketamine-related psychomimetic side effects.

Four clinical trials (61–64) with 5 treatment arms evaluated ketamine as adjuvant analgesic to opioids in children (Table 6). Two-hundred-thirty-two children were studied; 129 received ketamine. The route of ketamine administration varied, with IV ketamine given in 2 studies (63,64) and caudal (61) and IM ketamine (62) in one each. Two studies reported positive outcomes on postoperative analgesia (61,62) and 2 other studies reported no improvement in analgesia (63,64). The average quality scores of both positive and negative trials were 4.5. One positive trial and one negative trial mentioned power calculations. Different pain scales were used in each study, precluding quantitative analysis. Side effects were not increased by ketamine given as single bolus.

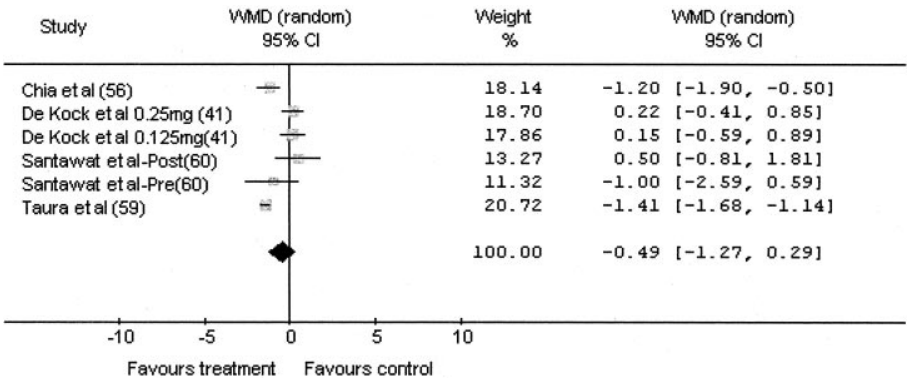

Figure 5. Epidural ketamine with epidural opioids (visual analog scale during movement). WMD = weighted mean difference; CI = confidence interval).

Intravenous ketamine continuous infusion was associated with increased CNS side effects in one study (63). No conclusions can be drawn regarding the use of ketamine as adjuvant analgesic in children.

Discussion

In this systematic review, we sought to analyze clinical trials on the efficacy and safety of adding small dose ketamine to perioperative opioid-based analgesia. To demonstrate analgesic efficacy, we used a combined qualitative and quantitative approach for data from randomized, double-blind clinical trials. Quantitative analysis was possible for VAS scores during the first 24 hours of the postoperative period. This was done to produce a single estimate of the effect of the intervention and to help resolve disparities between conflicting studies. The initial 24 hours was chosen because of the availability of data for most clinical trials, as well as the fact that the intensity of pain is maximal during the early postoperative period. WMD of 8.5, 8.2, and 7.1 mm were found in favor of ketamine co-analgesia for a single IV bolus, continuous IV infusion, and epidural ketamine, respectively. Although these differences are statistically significant, clinical relevance is minimal for this outcome measure taken alone.

The limitations of using WMD of VAS as an outcome measure are as follows: first, some trials did not report the actual VAS data and others did not report the dispersion measures needed for analysis. Second, not all clinical trials reported VAS on movement or during coughing/deep inspiration to calculate WMD. Third, VAS alone may not reflect the efficacy of the intervention because some studies aimed to maintain VAS less than 3–4 by analgesic supplementation at all times. In this case, VAS analysis may not show any difference between groups, but the total dose of supplemental analgesia will reflect the effect of the intervention. Only qualitative analysis was possible for other analgesic outcome measures such as TFA and TSD because of the variety of analgesia and doses used. For this reason, qualitative analysis of VAS and other outcome measures were combined with quantitative VAS analysis to provide a reasonable answer. Finally, control patients involved in this review were already receiving standard practice analgesia and were not deprived of pain medications, unlike meta-analysis of pain interventions compared with placebo. Thus, WMD of VAS was not able to detect a major difference between groups in this review.

Studies were divided into 5 subgroups based on the route and method of ketamine administration (IV ketamine as a single bolus dose, IV ketamine as a continuous infusion with IV and epidural opioids, IV ketamine with opioid in PCA, epidural ketamine with epidural opioids, and studies in pediatric population).

A significant number of clinical trials (17 of 38, 45%) demonstrated no benefit of adding ketamine to the existing standard practice opioid analgesia. This can be explained by the nature of surgical procedure, the degree of postoperative pain and the method of ketamine administration. In surgical procedures such as appendicectomy (64), tonsillectomy (63), laparoscopic surgery (52,53), and knee arthroscopy (36), standard practices with opioids, NSAIDs, and local anesthetic infiltration can provide adequate pain relief, so adding ketamine may not provide any additional benefit. Ketamine should be considered when postoperative pain requires large doses of opioids, such as major abdominal and thoracic surgery. Weinbroum (50) evaluated the role of ketamine in morphine-resistant pain. Patients were selected in the recovery room after morphine was given in adequate doses, but pain was still not controlled. The beneficial opioid-sparing effect was shown in these patients with acute opioid tolerance. Selection of these "difficult to manage" patients and a trial of ketamine may be a useful strategy in postoperative pain management. Another reason for the negative findings could be the method and dose of ketamine administration. Among the various methods of IV ketamine administration, continuous IV infusion of ketamine seems to be most helpful in major abdominal surgical procedures. In contrast to IV infusion, adding ketamine to IV PCA opioids was not helpful in 5 of 6 studies. Patients receiving infusions received relatively larger total doses of ketamine. Maintenance of steady blood levels with the continuous infusions

(5–10 mg/h) rather than repeated ultra small dose boluses (1–2 mg) as inpatient-dependent PCA administration may be important when using ketamine as an adjuvant with opioid-based analgesic regimens for postoperative analgesia in abdominal surgery.

Epidural ketamine produced impressive results whether administered as a single dose or as continuous infusion with PCEA. Ketamine is not approved by the Food and Drug Administration for epidural use because of its questionable neurotoxic effects. These have been attributed to the preservative (chlorbutanol); preservative-free ketamine is not available in the United States. De Lima et al. (65), in reviewing the neural toxicity of ketamine, encouraged the continued study of small doses (in small concentrations) of preservative-free ketamine through the epidural route. De Kock et al. (41) and Xie et al. (54) evaluated the appropriate route for the beneficial effect of ketamine as an additive. De Kock et al. used multimodal continuous epidural analgesia with ketamine, sufentanil, bupivacaine, epinephrine, and clonidine. The most valuable outcome of this study was the improvement in the area of wound hyperalgesia and chronic pain with IV ketamine. No difference was detectable in acute postoperative analgesic outcome measures between IV and epidural ketamine. They concluded that the IV route was the choice for ketamine as part of multimodal epidural analgesia. Aida et al. (42) concluded that using epidural morphine and IV ketamine as a continuous infusion throughout surgery blocks the noxious input at segmental and suprasegmental levels, respectively, and provides effective analgesia and prevents CNS sensitization in patients undergoing gastrectomy. However, this trial did not include epidural morphine with epidural ketamine as another group, as they believed that suprasegmental noxious inputs could only be blocked by IV ketamine. A study by Xie et al. (54) compared single doses of IV and epidural ketamine together with intraoperative IV fentanyl and postoperative PCEA morphine. They found a prolonged half-life, sustained large plasma concentrations, and superior analgesic effects with epidural ketamine. It remains to be seen whether a single dose of epidural ketamine can provide superior or comparable analgesia compared with continuous IV ketamine infusion with less side effects.

Beneficial effects of preemptive ketamine analgesia were based on presumed prevention of central sensitization by NMDA receptors (10). However, others feel that ketamine will be more effective after sufficient nociceptive stimulation has occurred to open the ligand gated ionic channels of NMDA receptors (66). In this review, both preincisional and postincisional administration of ketamine were found to be useful as adjuvant to opioids in comparable number of trials.

The effect of adding ketamine to opioids or multimodal analgesic regimens on wound hyperalgesia was tested in four clinical trials (31,35,41,43). Wound hyperalgesia was evaluated by punctuate mapping with Von Frey hair filaments and pressure pain detection thresholds. The area of hyperalgesia tested by Von Frey hair filament was significantly less in ketamine groups in 3 trials (31,35,41). The clinical implication of the area of hyperalgesia is poorly understood and not well studied. It is an indicator of central sensitization, and a reduction in the area of hyperalgesia could be a measure of the prevention of central sensitization by ketamine. Interestingly, the reduction in the area of hyperalgesia was not associated with improvement in acute postoperative pain outcome measures in any of the three studies. However, wind-up pain at 7 days was evaluated by Stubhaug et al. (35) and was reduced by ketamine. De Kock et al. (41) evaluated chronic persistent pain by a standardized telephone questionnaire regarding the nature and duration of pain and the analgesic requirements at 2 wk, 1 mo, 6 mo, and 1 yr after surgery. Patients who received IV ketamine had significantly reduced long-term pain. All patients studied by De Kock et al. (46) had undergone surgery for rectal adenocarcinoma. Thus, small dose ketamine may have a role in reducing pathological pain, which is chronic and neuropathic, even without any effect on acute nociceptive pain. Surgical procedures such as thoracotomy and amputation are associated with chronic postoperative neuropathic pain (67–69). These may be the ideal patient groups for studying the long-term effects of adding ketamine to opioid analgesia.

Cancer patients with chronic opioid intake develop tolerance and adverse effects. Ketamine has proved to be a useful adjuvant for the management of pain in these patients (70–72). However, the usefulness of ketamine in the management of acute postoperative pain in chronic opioid-tolerant patients has never been studied. Patients with chronic opioid intake for pain commonly undergo back surgery and amputation of extremities. This is an area of future research where ketamine may be useful for its opioid-sparing effect.

The incidences of various central nervous system side effects (dizziness, diplopia, dysphoria, dreams, hallucinations disorientation, strange sensations, light headedness, sleep difficulties, and confusion) in ketamine-treated patients were 18%, 10%, 9%, and 0.7% with IV PCA, IV infusion, IV single dose, and epidural groups. No significant increase was seen compared to patients who did not receive ketamine. A trend toward less PONV was seen in IV ketamine bolus and infusion group patients. These reductions in PONV parallel the decreased opioid consumption and improved analgesia in these groups. Respiratory depression was reported in 9 patients; 5 of them received ketamine plus opioids. As the incidence of narcotic-induced respiratory depression is very small, it is difficult to demonstrate any effect of ketamine. In this

review, pruritus was reported as a major side effect (45.6%) of epidural opioids and ketamine did not reduce the incidence of pruritus significantly in these patients.

In conclusion, small dose ketamine has been shown to be a useful and safe additive to standard practice opioid analgesia in 54% of studies. Both systemic and epidural ketamine have shown their beneficial opioid-sparing effects. Ketamine should be considered as an additive in the surgical population with large opioid requirements, such as major abdominal surgery. Intravenous ketamine is best used as continuous infusion in these patients. Adding ketamine to PCA morphine has not been found to be useful. In minor surgical procedures, a single dose of ketamine ranging from 0.15–1 mg/kg in addition to opioids may be useful. Despite ketamine's opioid-sparing effects, no reduction in opioid-related side effects such as PONV, pruritus, and respiratory depression could be shown in this review. Small dose ketamine was not associated with increased psychomimetic effects such as hallucinations or excessive sedation. Future clinical trials should focus on high-risk groups for opioid-resistant acute postoperative pain (chronic therapeutic opioid intake, substance abusers, amputations, and back surgeries) and on the influence of small dose ketamine used for acute postoperative pain on long-term pain syndromes (postmastectomy, thoracotomy, and phantom pain).

References

1. Clausen L, Sinclair DM, Van Hasselt CH. Intravenous ketamine for postoperative analgesia. S Afr Med J 1975;49:1437–40.
2. Jahangir SM, Islam F, Chowdhury SN, et al. Ketamine infusion for postoperative analgesia: a prospective cohort study in asthmatics. Bangladesh Med Res Counc Bull 1993;19:21–7.
3. Jahangir SM, Islam F, Aziz L. Ketamine infusion for postoperative analgesia in asthmatics: a comparison with intermittent meperidine. Anesth Analg 1993;76:45–9.
4. Dich-Nielsen JO, Svendsen LB, Berthelsen P. Intramuscular low-dose ketamine versus pethidine for postoperative pain treatment after thoracic surgery. Acta Anaesthesiol Scand 1992;36: 583–7.
5. Bhattacharya A, Gurnani A, Sharma PK, Sethi AK. Subcutaneous infusion of ketamine and morphine for relief of postoperative pain: a double blind comparative study. Ann Acad Med Singapore 1994;23:456–9.
6. Owen H, Reekie RM, Clements JA, et al. Analgesia from morphine and ketamine: a comparison of infusions of morphine and ketamine for postoperative analgesia. Anaesthesia 1987;42: 1051–6.
7. Mankowitz E, Downing JW, Brock-Utne JG, et al. Total intravenous anaesthesia using low-dose ketamine infusion for caesarean section: a comparison with a standard inhalation anaesthetic technique. S Afr Med J 1984;65:246–50.
8. Kawana Y, Sato H, Shimada H, et al. Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. Anesth Analg 1987;66:735–8.
9. Peat SJ, Bras P, Hanna MH. A double-blind comparison of epidural ketamine and diamorphine for postoperative analgesia. Anaesthesia 1989;44:555–8.
10. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartate acid receptor activation: implication for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–9.
11. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995;62:259–74.
12. Kissin I, Bright CA, Bradley EL Jr. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anesth Analg 2000;91:1483–8.
13. Celerier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology 2000;92:465–72.
14. Laulin JP, Maurette P, Corcuff JB, et al. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg 2002;94:1263–9.
15. Rivat C, Laulin JP, Corcuff JB, et al. Fentanyl enhancement of carrageenan-induced long-lasting hyperalgesia in rats: prevention by the *N*-methyl-D-aspartate receptor antagonist ketamine. Anesthesiology 2002;96:381–91.
16. Adam F, Libier M, Oszustowicz T, et al. Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesth Analg 1999;89:444–7.
17. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997;84:1086–90.
18. Kucuk N, Kizilkaya M, Tokdemir M. Preoperative epidural ketamine does not have a postoperative opioid sparing effect. Anesth Analg 1998;87:103–6.
19. Holthusen H, Backhaus P, Boeminghaus F, et al. Preemptive analgesia: no relevant advantage of preoperative compared with postoperative intravenous administration of morphine, ketamine, and clonidine in patients undergoing transperitoneal tumor nephrectomy. Reg Anesth Pain Med 2002;27:249–53.
20. Wu CT, Yeh CC, Yu JC, et al. Preincisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anaesthesiol Scand 2000;44:63–8.
21. Choe H, Choi YS, Kim YH, et al. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. Anesth Analg 1997;84:560–3.
22. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can J Anaesth 1997;44:31–7.
23. Jaded AR, Moore A, Carrol D et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–12.
24. L' Abbe K, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987;107:224–33.
25. Bristow A, Orlikowski C. Subcutaneous ketamine analgesia: postoperative analgesia using subcutaneous infusions of ketamine and morphine. Ann R Coll Surg Engl 1989;71:64–6.
26. Wong CS, Liaw WJ, Tung CS, et al. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Reg Anesth 1996;21:534–41.
27. Parkhouse J, Marriott G. Postoperative analgesia with ketamine and pethidine. Anaesthesia 1977;32:285–9.
28. Reeves M, Lindholm DE, Myles PS, et al. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesth Analg 2001;93:116–20.
29. Hercock T, Gilham MJ, Sleigh J, Jones SF. The addition of ketamine to patient controlled morphine analgesia does not improve quality of analgesia after total abdominal hysterectomy. Acute Pain 1999;2:68–72.
30. Murdoch CJ, Crooks BA, Miller CD. Effect of the addition of ketamine to morphine in patient-controlled analgesia. Anaesthesia 2002;57:484–8.

31. Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care 2001;29:246–51.
32. Unlugenc H, Ozalevli M, Guler T, Isik G. Postoperative pain management with intravenous patient controlled morphine: comparison of the effect of adding magnesium or ketamine. Eur J Anaesthesiol 2003;20:416–21.
33. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996;43:212–5.
34. Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia 1993;48:124–7.
35. Stubhaug A, Breivik H, Eide PK, et al. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124–32.
36. Adriaenssens G, Vermeyen KM, Hoffmann VL, et al. Postoperative analgesia with IV patient-controlled morphine: effect of adding ketamine. Br J Anaesth 1999;83:393–6.
37. Jaksch W, Lang S, Reichhalter R, et al. Perioperative small-dose S (+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. Anesth Analg 2002;94:981–6.
38. Guignard B, Coste C, Costes H, et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg 2002;95:103–8.
39. Heinke VW, Grimm D. Preemptive effects through co analgesia with ketamine in gynaecological laparotomies? Anaesthesiol Reanimat 1999;24:60–4.
40. Guillou N, Tanguy M, Seguin P, et al. The effects of small dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg 2003;97:843–7.
41. De Kock M, Lavand'Homme P, Waterloos H. "Balanced analgesia" in the perioperative period: is there a place for ketamine? Pain 2001;92:373–80.
42. Aida S, Yamakura T, Baba H, et al. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology 2000;92:1624–30.
43. Ilkjaer S, Nikolajsen L, Hansen TM, et al. Effect of IV ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth 1998;81:707–12.
44. Karamaz A, Kaya S, Karaman H, et al. Intraoperative intravenous ketamine in combination with epidural analgesia: Postoperative analgesia after renal surgery. Anesth Analg 2003;97:1092–6.
45. Suzuki M, Tsueda K, Lansing PS, et al. Small-dose ketamine enhances morphine-induced analgesia after outpatient surgery. Anesth Analg 1999;89:98–103.
46. Menigaux C, Guignard B, Fletcher D, et al. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. Anesth Analg 2001;93:606–12.
47. Menigaux C, Fletcher D, Dupont X, et al. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg 2000;90:129–35.
48. Roytblat L, Korotkoruchko A, Katz J, et al. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg 1993;77:1161–5.
49. Dahl JB, Ernoe PE, Steen T, et al. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg 2000;90:1419–22.
50. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg 2003;96:789–95.
51. Kudoh A, Takahira Y, Katagai H, et al. Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002;95:114–8.
52. Mathisen LC, Assbo Y, Raeder J. Lack of pre-emptive analgesic effect of (R)-ketamine in laparoscopic cholecystectomy. Acta Anaesth Scand 1999;43:220–4.
53. Lehmann KA, Klaschik M. Lack of pre-emptive analgesic effect of low-dose ketamine in postoperative patients: a prospective, randomized double-blind study. Schmerz 2001;15:248–53.
54. Xie H, Wang X, Liu G, Wang G. Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously. Clin J Pain 2003;19:317–22.
55. Tan PH, Kuo MC, Kao PF, et al. Patient-controlled epidural analgesia with morphine or morphine plus ketamine for postoperative pain relief. Eur J Anaesthesiol 1999;16:820–5.
56. Chia YY, Liu K, Liu YC, et al. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesth Analg 1998;86:1245–9.
57. Subramaniam B, Subramaniam K, Pawar DK, Sennaraj B. Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra- and postoperative opioid-sparing effect. Anesth Analg 2001;93:1321–6.
58. Subramaniam K, Subramaniam B, Pawar DK, Kumar L. Evaluation of the safety and efficacy of epidural ketamine combined with morphine for postoperative analgesia after major upper abdominal surgery. J Clin Anesth 2001;13:339–44.
59. Taura P, Fuster J, Blasi A, et al. Postoperative pain relief after hepatic resection in cirrhotic patients: the efficacy of a single small dose of ketamine plus morphine epidurally. Anesth Analg 2003;96:475–80.
60. Santawat U, Pongraweewan O, Lertakayamanee J, et al. Can ketamine potentiate the analgesic effect of epidural morphine, preincisional or postincisional administration? J Med Assoc Thai 2002;85:S1024–30.
61. Ozbek H, Bilen A, Ozcengiz D, et al. The comparison of caudal ketamine, alfentanil and ketamine plus alfentanil administration for postoperative analgesia in children. Paediatr Anaesth 2002;12:610–6.
62. Elhakim M, Khalafallah Z, El-Fattah HA, et al. Ketamine reduces swallowing-evoked pain after pediatric tonsillectomy. Acta Anaesthesiol Scand 2003;47:604–9.
63. O'Flaherty JE, Lin CX. Does ketamine or magnesium affect post-tonsillectomy pain in children? Paediatr Anaesth 2003;13:413–21.
64. Dix P, Martindale S, Stoddart PA. Double blind randomized placebo-controlled trial of the effect of ketamine on postoperative morphine consumption in children following appendicectomy. Paediatr Anaesth 2003;13:422–6.
65. De Lima J, Beggs S, Howard R. Neural toxicity of ketamine and other NMDA antagonists. Pain 2000;88:311–2.
66. Arendt-Nielsen L, Petersen-Felix S, Fisher M, et al. The effect of *N*-methyl-D-aspartate (ketamine) on single and repeated nociceptive stimuli; a placebo controlled experimental human study. Anesth Analg 1995;81:63–8.
67. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: A review of predictive factors. Anesthesiology 2000;93:1123–33.
68. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow up study. Acta Anaesthesiol Scand 1999;43:563–7.
69. Wartan SW, Hamann W, Wedley JR, et al. Phantom pain and sensation among British veteran amputees. Br J Anaesth 1997;78:652–9.
70. Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2003;1:CD003351.
71. McQueen AL, Baroletti SA. Adjuvant ketamine analgesia for the management of cancer pain. Ann Pharmacother 2002;36:1614–9.
72. Kannan TR, Saxena A, Bhatnagar S, Barry A. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. J Pain Symptom Manage 2002;2:60–5.