British Journal of Anaesthesia **83 (3)**: 393–6 (1999)

Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine

G. Adriaenssens, K. M. Vermeyen*, V. L. H. Hoffmann, E. Mertens and H. F. Adriaensen

University Hospital Antwerp, Department of Anaesthesia, Wilrijkstraat 10, B-2650 Edegem, Belgium

**Corresponding author*

We have studied the effect of adding ketamine to i.v. morphine patient-controlled analgesia (PCA) for the treatment of pain after laparotomy. Thirty patients were allocated randomly to receive PCA with saline or ketamine in a double-blind, randomized study. Analgesia was started in the recovery room when visual analogue scale (VAS) scores were >4. A bolus dose of morphine 3 mg was given to all the patients followed by i.v. PCA. Simultaneously, an infusion of ketamine 2.5 μg kg^{-1} min^{-1} or saline was started. Pain scores, morphine consumption and side effects were noted for up to 48 h after the start of PCA. VAS scores decreased significantly with time (P= 0.0001) and were similar (P= 0.3083) in both groups. Cumulative morphine consumption at 48 h was significantly lower in the ketamine group (28 mg) than in the control group (54 mg) (P= 0.0003). Nausea was less frequent in the ketamine group (P=0.03).

Br J Anaesth 1999; **83**: 393–6

Keywords: analgesia, patient-controlled; analgesics opioid, morphine; anaesthetics i.v., ketamine; pain, postoperative; surgery, laparotomy

Accepted for publication: March 3, 1999

Morphine is used widely in the treatment of pain but it may be associated with significant side effects such as respiratory depression, urinary retention, nausea and vomiting, sedation and prolonged postoperative ileus.[1] Good control of postoperative pain with a reduced incidence of side effects has been reported with patient-controlled analgesia (PCA).[2]

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has analgesic properties in subanaesthetic doses.[3] Psychomimetic side effects, however, have been a major problem when used for postoperative analgesia.[3 4] The combination of morphine with ketamine has been shown to result in increased analgesic effect, which may be synergistic or additive.[5] The analgesic effect of ketamine given as a continuous infusion has been observed at plasma concentrations of 100–150 ng ml^{-1}.[5–7]

In this double-blind, randomized study, we have investigated the quality of postoperative analgesia after laparotomy with a combination of morphine (i.v. PCA) and ketamine at doses likely to produce plasma concentrations of 100 mg ml^{-1}, compared with morphine (i.v. PCA) alone.

Patients and methods

After obtaining approval from the Local Ethics Committee and informed consent, we studied 30 patients (ASA I–III) undergoing abdominal surgery, allocated randomly to receive i.v. PCA morphine with saline (control group) or ketamine (ketamine group). Before operation, patients were instructed on the use of a PCA and the visual analogue scale (VAS: 0=no pain, 10=worst pain imaginable).

All patients were premedicated with sublingual lorazepam 2.5 mg, 90 min before operation. A central venous catheter (internal jugular vein), two peripheral i.v. catheters and an arterial catheter (radial artery) were inserted. Monitoring consisted of ECG, pulse oximetry, invasive arterial pressure, central venous pressure, capnography and body temperature. General anaesthesia was induced with fentanyl 2 μg kg^{-1}, propofol 1.5–2 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide, isoflurane and vecuronium. Increments of fentanyl were administered if considered necessary by the attending anaesthetist. After operation, patients stayed in the post-anaesthesia care unit for 24 h.

When a VAS score of 4 was reached, a loading dose of morphine 3 mg followed by another dose of 3 mg, 45 min later, were given. The PCA device, containing morphine 1 mg ml^{-1}, was started in both groups. Patients were allowed to ask for a bolus dose of morphine 1 mg every 8 min, but with a 1-h limit of 5 mg.

Patients were allocated randomly to receive a continuous infusion of saline (control group) or ketamine (ketamine group), which was started together with a loading dose of morphine. The infusion rate of ketamine was calculated using a pharmacokinetic computer simulation (Stanpump; Stanpump is freely available from Steven L. Shafer, MD,

Table 1 Patient data (mean (range)). No significant differences

	Ketamine group ($n=15$)	**Control group ($n=15$)**
Sex (F:M)	13:2	10:5
Age (yr)	53 (27–83)	51 (17–82)
Weight (kg)	76 (49–120)	71 (46–114)
Duration of surgery (min)	195 (89–300)	187 (90–270)
Surgery: laparotomy (*n*)		
Gastrointestinal	5	11
Urological	7	3
Gynaecological	3	1

Anesthesiology Service (112A) PAVAMC, 3801 Miranda Ave, Palo Alto, CA 94304, USA)[8 9] and was set to produce a theoretical plasma concentration of 100 ng ml^{-1}. This concentration has been shown to provide analgesia without important side effects.[7] The initial rate was 10 μg kg^{-1} min^{-1}, decreasing to 7.5 μg kg^{-1} min^{-1} after 5 min. After 30 and 45 min, the infusion rate was decreased further to 5 and 2.5 μg kg^{-1} min^{-1}, respectively, and was then maintained at 2.5 μg kg^{-1} min^{-1} for 48 h.

Arterial pressure, heart rate, ventilatory frequency, pain score, morphine consumption and side effects were evaluated at 0, 1, 2, 4, 6, 12, 24, 36 and 48 h after the PCA device had been started. On day 3 after operation, patients were asked if they had experienced any of the following: nausea, dreams, hallucinations, blurred vision, dizziness, agitation, co-ordination disturbances, sedation or oral secretions.

To detect a difference of 25% in morphine consumption at the 0.05 level of significance (α) with a power of 0.90, a minimum of 15 patients were required in each group. A sample of this size had a power of 0.85 ($\alpha=0.05$) to detect a difference in the incidence of side effects. Analysis of variance (ANOVA) followed by *post hoc* testing using the Sheffé *F* test, paired Student's *t* test and Mann–Whitney *U* test were used for statistical analysis where appropriate. $P<0.05$ was considered statistically significant.

Results

The groups were similar in sex, age, weight, type of surgery and duration of surgery (Table 1). Heart rate, systolic arterial pressure and ventilatory frequency were comparable in both groups (Table 2).

VAS scores decreased significantly with time in both groups ($P=0.0001$). Mean pain score at rest after 1 h was significantly lower in the ketamine group ($P=0.0101$) compared with the control group (Table 3). At all other times, pain scores were similar.

Morphine consumption differed significantly between the control and ketamine groups (Table 3). During the first 12 h, cumulative and incremental postoperative morphine consumption were similar in both groups. At 24, 36 and 48 h, cumulative and incremental morphine consumption were significantly less in the ketamine group.

Mean cumulative consumption of morphine differed significantly between groups after 24 h and the difference increased with time. After 48 h, morphine requirements in the control group were almost twice those of the ketamine group. This difference was highly significant ($P=0.0003$) (Table 3, Fig. 1). Mean incremental morphine consumption in the control group remained approximately 1.0 mg h^{-1} while it decreased to 0.2 mg h^{-1} in the ketamine group ($P=0.0002$ at 48 h) (Table 3).

There was a trend to less side effects in the ketamine group ($P=0.09$) (Table 4) and the number of patients reporting side effects also tended to be lower in the ketamine group ($P=0.07$). The incidence of nausea in the ketamine group differed significantly from the control group ($P=0.03$). Diplopia, a typical ketamine-related side effect, was reported by two patients. No hallucinations were reported.

Discussion

We have demonstrated that postoperative pain after laparotomy can be treated successfully with a low-dose continuous infusion of ketamine supplemented with i.v. morphine PCA. The combination of ketamine and morphine allowed a significant reduction in morphine consumption and decreased incidence of nausea. The dose of ketamine was low enough to avoid its psychomimetic effects.

Our data are similar to those of Javery and colleagues.[5] However, we investigated the time course of VAS pain scores and morphine consumption, both cumulative and incremental. Edwards and colleagues[10] used a dose-finding approach to study the combination of morphine and ketamine for postoperative pain in elderly patients and found dreams to be a problem at higher ketamine doses. The maximum dose was 7.8 μg kg^{-1} min^{-1}, substantially higher than that in our study (2.5 μg kg^{-1} min^{-1}). Morphine consumption was the same with or without ketamine. This finding may be explained by the fact that PCA was started immediately after surgery, while in our study it was started after a VAS score of 4 was reported by the patient. This may be important as the effect of NMDA block may only be apparent after the receptor-operated ion channel has been opened by nociceptive stimulation.[11 12] The importance of the level of initial nociception to distinguish between treatments has been emphasized recently by Kalso.[13]

Prolonged sensory afferent activation (C-fibres) is associated with spinally released peptides in association with glutamate to activate NMDA receptors. This activation leads to neuronal excitation (hyperalgesia, 'wind-up'). NMDA receptor antagonists abolish this 'wind-up' while opioids only delay the onset of NMDA receptor activation without inhibiting the process itself.[12] Therefore, it seems logical to combine morphine with ketamine for acute pain treatment and to use ketamine pre-emptively. However, studies on the pre-emptive use of ketamine, administered both i.v. or epidurally, are not conclusive,[14–17] perhaps because of the difference in pain intensity experienced by patients before operation.

Table 2 Clinical variables (mean (SD) [range]) in the ketamine ($n=15$) and control ($n=15$) groups (P values ANOVA)

	Heart rate (beat min^{-1})			Systolic arterial pressure (mm Hg)			Ventilatory frequency (bpm)		
Time (h)	**Ketamine**	**Control**	***P***	**Ketamine**	**Control**	***P***	**Ketamine**	**Control**	***P***
0	87 (21) [63–124]	84 (16) [53–112]	0.76	129 (17) [104–164]	137 (23) [106–178]	0.26	18 (2) [14–23]	19 (3) [14–25]	0.50
1	84 (20) [55–107]	84 (12) [67–109]	0.98	123 (19) [91–154]	131 (16) [110–190]	0.25	17 (3) [14–24]	17 (4) [13–26]	0.79
2	82 (18) [58–127]	86 (13) [67–112]	0.48	129 (20) [100–168]	132 (20) [105–166]	0.67	17 (3) [11–20]	17 (4) [11–28]	0.72
4	87 (15) [60–112]	94 (14) [72–126]	0.21	131 (19) [105–155]	134 (23) [100–167]	0.63	18 (3) [13–24]	16 (3) [12–23]	0.21
6	88 (17) [64–127]	93 (11) [68–116]	0.29	131 (19) [101–160]	135 (21) [104–180]	0.61	17 (4) [10–26]	16 (2) [12–19]	0.29
12	88 (11) [72–104]	94 (12) [72–116]	0.21	130 (18) [105–160]	134 (22) [109–190]	0.52	17 (3) [13–24]	17 (4) [12–24]	0.73
24	86 (12) [70–104]	88 (8) [76–100]	0.53	129 (17) [105–155]	134 (16) [110–170]	0.43	17 (3) [14–24]	17 (2) [13–21]	0.48
36	88 (13) [67–112]	90 (10) [67–108]	0.78	130 (15) [110–160]	133 (18) [110–180]	0.12	17 (3) [14–27]	16 (2) [12–21]	0.28
48	84(12) [60–104]	87 (9) [68–104]	0.41	133 (13) [110–155]	134 (21) [105–180]	0.88	17 (3) [15–24]	16 (2) [12–2]	0.17

Table 3 Pain assessment and morphine consumption (mean (SD) [range]) in the ketamine ($n=15$) and control ($n=15$) groups. *$P<0.05$ (ANOVA)

	Visual analogue scale (mm)			Morphine cumulative (mg)			Morphine incremental		
Time (h)	**Ketamine**	**Control**	***P***	**Ketamine**	**Control**	***P***	**Ketamine**	**Control**	***P***
0	5.9 (2.1) [4–10]	6.7 (2.1) [4–9]	0.34	0.1 (0.4) [0–1]	0.3 (0.8) [0–3]	0.56	–	–	–
1	2.5 (3.0) [1–9]	5.4 (2.8) [1–10]	0.01*	0.3 (0.7) [0–2]	0.5 (1.1) [0–4]	0.57	0.3 (0.8) [0–1]	0.8 (1.9) [0–2]	0.38
2	2.9 (2.5) [1–7]	4.3 (2.9) [1–8]	0.17	1.7 (2.3) [0–7]	3.1 (2.6) [0–7]	0.11	1.5 (1.8) [0–6]	2.7 (2.2) [0–7]	0.12
4	3.1 (2.5) [1–8]	3.2 (2.4) [1–6]	0.86	3.3 (3.7) [0–13]	5.5 (4.5) [0–14]	0.14	1.2 (1.3) [0–6]	1.3 (1.3) [0–10]	0.84
6	2.3 (2.3) [1–7]	3.0 (2.5) [1–9]	0.46	5.8 (6.3) [0–20]	9.5 (5.9) [0–21]	0.10	1.1 (1.4) [0–18]	1.9 (1.6) [1–18]	0.15
12	2.6 (2.7) [1–9]	2.8 (1.7) [1–5]	0.82	11.5 (9.4) [0–32]	16.5 (9.8) [1–39]	0.17	1.0 (0.9) [0–18]	1.4 (0.8) [1–18]	0.21
24	2.5 (1.8) [1–5]	3.6 (2.4) [1–7]	0.18	19.4 (10.7) [2–44]	30.7 (15.9) [8–67]	0.03*	0.6 (0.5) [1–19]	1.2 (0.6) [4–33]	0.003*
36	1.9 (1.7) [1–5]	2.9 (1.8) [1–7]	0.15	25.3 (12.5) [2–45]	43.2 (16.8) [12–79]	0.003*	0.5 (0.4) [0–16]	0.9 (0.5) [2–18]	0.03*
48	1.2 (1.3) [1–5]	2.1 (1.8) [1–7]	0.1491	27.6 (12.4) [5–45]	54.1 (21.9) [12–88]	0.0003*	0.2 (0.2) [0–9]	1.0 (0.6) [0–28]	0.0002*

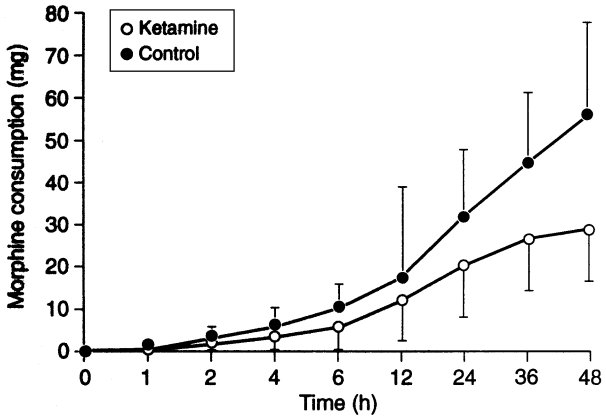

Fig 1 Mean cumulative morphine consumption in the ketamine and control groups (mean (SD)).

Table 4 Incidence of side effects in the ketamine and control groups. *$P<0.05$

	Ketamine group ($n=15$)	**Control group ($n=15$)**	***P***
Dreams	1	1	0.46
Secretions	1	0	0.31
Nausea	1	6	0.03*
Vomiting	1	2	0.54
Diplopia	2	0	0.14
Sedation	0	2	0.14
Hallucinations	0	0	–
Total	6	11	0.09
No. of patients reporting side effects	4	9	0.07

Ketamine, in combination with opioids, has been used epidurally with similar results.[16 18 19] Human experience with intrathecal use of ketamine or other NMDA receptor antagonists is limited to a few case reports relating to chronic pain treatment.[20 21]

Possible mechanisms explaining our results include summation of analgesia, synergy and prevention of acute tolerance to morphine. Summation is supported by the consistently smaller morphine consumption in the presence of ketamine with similar VAS ratings. Furthermore, a synergistic effect of morphine and ketamine is possible. The temporal change of incremental morphine consumption in the ketamine group differed from that in the control group. This may indicate a different underlying mechanism. However, our method did not allow for any conclusion in this regard as we did not use different doses of morphine and ketamine in a crossover study. A third mechanism relates to the development of acute tolerance to morphine and its prevention by ketamine. In rats, acute tolerance to i.v. administered opioids develops within hours.[22] Acute tolerance after 24 h of morphine infusion for postoperative pain treatment in humans has been reported.[23] In a study comparing continuous infusion of morphine with bolus injections, Marshall and colleagues[24] proposed the development of tolerance to explain his results. The ability of NMDA receptor blocking agents to prevent development of acute tolerance has been demonstrated in mice.[25] The consistently increasing difference in morphine consumption between the ketamine and control groups in our study may be the result of this phenomenon.

Further research is necessary to explain the underlying mechanisms of our results. A study of the impact of the combination of morphine and ketamine on outcome and hospital stay would reveal the clinical importance of this technique.

References

1 Brown JG. Systemic opioid analgesia for postoperative pain management. *Anesthesiol Clin N Am* 1989; **7**: 51–62

2 White PF. Use of patient-controlled analgesia for management of acute pain. *JAMA* 1988; **259**: 243–7

3 Eide PK, Stubhaug A, Oye I. The NMDA-antagonist ketamine for prevention and treatment of acute and chronic postoperative pain. *Baillieres Clin Anesthesiol* 1995; **9**: 539–54

4 Ito Y, Ichiyanagi K. Postoperative pain relief with ketamine infusion. *Anaesthesia* 1974; **29**: 222–9

5 Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. *Can J Anaesth* 1996; **43**: 212–15

6 Grant IS, Nimmo WS, Clements JA. The pharmacological and analgesic effects of intramuscular and oral ketamine. *Br J Anaesth* 1981; **53**: 805–10

7 Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; **53**: 27–30

8 Shafer SL, Gregg KM. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. *J Pharmacokinet Biopharm* 1992; **20**: 147–69

9 Domino EF, Zsigmond EK, Domino LE, Domino KE, Kothary SP, Domino SE. Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. *Anesth Analg* 1982; **61**: 87–92

10 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

11 Arendt-Nielsen L, Petersen-Felix S, Fisher M, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo controlled experimental human study. *Anesth Analg* 1995; **81**: 63–8

12 Dickenson AH. NMDA receptor antagonists: interaction with opioids. *Acta Anaesthesiol Scand* 1997; **41**: 112–15

13 Kalso E. Better standardisation will improve the quality of analgesic studies. *Acta Anaesthesiol Scand* 1996; **40**: 397–8

14 Tverskoy M, Isakson A, Finger J, Bradley EL, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesth Analg* 1994; **78**: 205–9

15 Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. *Anesth Analg* 1997; **84**: 1068–90

16 Choe H, Choi YS, Kim YH, Choi HG, Han YJ, Song HS. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. *Anesth Analg* 1997; **84**: 560–3

17 Kucuk N, Kizilkaya M, Tokdemir M. Preoperative epidural ketamine does not have a postoperative opioid sparing effect. *Anesth Analg* 1998; **87**: 103–6

18 Yuan-Yi C, Kang L, Yuan-Chin L, Huang-Chou C, Chih-Shung W. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. *Anesth Analg* 1998; **86**: 1245–9

19 Abdel-Ghaffar ME, Abdulatif M, Al-Ghamdi A, Mowafi H, Anwar A. Epidural ketamine reduces post-operative epidural PCA consumption of fentanyl/bupivacaine. *Can J Anaesth* 1998; **45**: 103–9

20 Karpinsky N, Dunn J, Hansen L, Masliah E. Subpial vacuolar myelopathy after intrathecal ketamine: report of a case. *Pain* 1997; **73**: 103–5

21 Kristensen JD, Svensson B, Gordh T. The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. *Pain* 1992; **51**: 249–53

22 Kissin I, Brown PT, Robinson A, Bradley EL. Acute tolerance in morphine analgesia: continuous infusion and single injection in rats. *Anesthesiology* 1991; **74**: 166–71

23 McQuay HJ, Bullingham RES, Moore RA. Acute opiate tolerance in man. *Life Sci* 1981; **28**: 2513–17

24 Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? *BMJ* 1985; **291**: 19–21

25 Trujillo KA, Akil H. Inhibition of opiate tolerance by non-competitive N-methyl-D-aspartate receptor antagonists. *Brain Res* 1994; **633**: 178–88