

The Addition of a Small-Dose Ketamine Infusion to Tramadol for Postoperative Analgesia: A Double-Blinded, Placebo-Controlled, Randomized Trial After Abdominal Surgery

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BACKGROUND: There are few data on combining ketamine with tramadol for postoperative analgesia in humans. We tested the hypothesis that adding ketamine to tramadol would improve analgesia after major abdominal surgery.

METHOD: In this double-blind, randomized, controlled trial, adult patients ($n = 120$) having elective laparotomy were randomly assigned to a ketamine group (intraoperative ketamine 0.3 mg/kg and postoperative infusion at $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) or control group (equivalent volume/rate of normal saline). All patients received intraoperative tramadol 3 mg/kg and a tramadol infusion ($0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) for 48 h postoperatively and had morphine patient-controlled analgesia available for rescue analgesia.

RESULTS: The ketamine group had less pain at rest ($P = 0.01$) and with movement ($P = 0.02$) and required less morphine ($P = 0.003$) throughout the 48-h study period. In the 0–24 h period, ketamine improved subjective analgesic efficacy ($P = 0.008$), was less sedating ($P = 0.03$), and required fewer physician interventions to manage severe pain ($P = 0.01$). Hallucinations were more common in ketamine patients, but other side effects were similar.

CONCLUSION: Small-dose ketamine was a useful addition to tramadol and morphine after major abdominal surgery.

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There are considerable data supporting the addition of ketamine to morphine for postoperative pain (1–5). After major surgery, tramadol combined with morphine patient-controlled analgesia (PCA) was morphine-sparing and improved analgesia compared with morphine PCA alone (6). Human studies on the analgesic efficacy of combining ketamine and tramadol infusions are lacking. PCA ketamine/tramadol combinations have been compared with tramadol PCA alone in one small trial finding improved early postoperative analgesia (7). Coadministration of ketamine and tramadol in mice achieved synergistic antinociception in a chemically-induced persistent pain model, but not in acute thermal or chemical pain models (8). This study investigated whether analgesia improved when a small-dose ketamine infusion was added to a tramadol infusion/morphine PCA combination after major surgery.

METHODS

One hundred twenty adults having elective major abdominal surgery were recruited to this double-blind, randomized, controlled trial. Institutional ethics committee approval was given and written consent obtained from patients. Allocation to treatment group was determined in advance according to tables of random numbers and concealed from patients and hospital staff, using sealed opaque envelopes.

Patients were ASA physical status I–III, aged 19–89 yr, and weighed 41–117 kg. Several surgeons and anesthesiologists managed study subjects and most patients (91%) had upper abdominal incisions. Exclusion criteria included chronic pain, chronic opioid usage, inability to use a PCA, or any contraindication to tramadol, ketamine, or morphine.

Study medications were prepared in advance and transferred to the blinded anesthesiologist in the operating room. Randomization was to one of the following two groups:

1. Ketamine group: IV ketamine initial dose of 0.3 mg/kg at anesthetic induction and a ketamine infusion at $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 48 h or
2. Control group: An equivalent volume of normal saline at induction followed by a normal saline infusion at equivalent rate to maintain blinding.

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Table 1. Patient and Perioperative Characteristics

	Ketamine (<i>n</i> = 56)	Control (<i>n</i> = 64)	<i>P</i>
Age (yr)	63 ± 15	61 ± 15	0.94
Gender M/F	35/21 (63/37%)	39/25 (61/39%)	0.9
Weight (kg)	75 ± 15	75 ± 15	0.9
ASA physical status			
I	16 (29%)	14 (22%)	
II	36 (64%)	40 (62%)	
III	4 (7%)	10 (16%)	0.3
Current smoker	7 (13%)	21 (33%)	0.02
Site of surgery	111	111	
Upper abdomen	53 (95%)	57 (89%)	
Lower abdomen	3 (5%)	7 (11%)	0.3
Duration of surgery (min)	132 (45–330)	150 (70–450)	0.3
Duration in PACU (min)	80 (45–320)	88 (30–210)	0.3
Duration in hospital (days)	9 (4–25)	9 (5–28)	0.9
Intraoperative morphine (mg)	11 ± 5	13 ± 5	0.08
Intraoperative fentanyl (μg)	78 ± 64	64 ± 69	0.2
Morphine given in PACU (mg)	5 ± 7	7 ± 7	0.14

Values are mean ± sd, proportion (%), or median (range).

PACU = postanesthesia care unit.

All patients received an initial tramadol dose after induction (3 mg/kg) and tramadol infusion (0.2 mg · kg⁻¹ · h⁻¹) for 48 h. Anesthesia was induced with propofol. Muscle relaxation was maintained with atracurium, cisatracurium, or rocuronium. Anesthesia was maintained with isoflurane or sevoflurane, supplemented with intraoperative administration of IV fentanyl and/or morphine.

In the postanesthesia care unit, patients were given IV morphine boluses according to institutional protocol to achieve a pain score on the 11 point (0–10) verbal rating scale (VRS) of <4. Morphine PCA delivering a 1-mg bolus and 5-min lockout time was connected on discharge from the postanesthesia care unit to manage pain uncontrolled by study medications and continued throughout the 48-h study period. Thus, patients had three separate mechanical infusion devices during the study.

Other intraoperative or postoperative analgesics were not permitted, including local anesthetics, non-steroidal antiinflammatory medications, and acetaminophen. Patients with inadequate analgesia had PCA morphine boluses increased to 2 mg. Background infusions of morphine (1–2 mg/h) were permitted if analgesia remained suboptimal. Such analgesic interventions were recorded. Persistent resting VRS >4 resulted in patient withdrawal.

The study's primary end point was improvement in subjective analgesic efficacy (SAE) in which patients were asked, "How effective was your medication in relieving your pain over the last 24 h?" with responses: 1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, and 5 = very poor. Assessments were made at 24 and 48 h postoperatively. Pain scores (VRS) were recorded 4-hourly at rest and with movement for 48 h. Movement pain was defined by pain on rolling, sitting, or coughing. PCA morphine use was recorded at 24 and 48 h.

Side effects were assessed by sedation score, nausea score, antiemetic use, and sleep quality score (Appendix

A). Arterial blood pressure, heart rate, and respiratory rate data were collected. Patients were questioned daily about vivid dreams or hallucinations. Cognitive testing was performed with the Trail Making Test (Part B) in which patients were asked to draw a continuous line connecting mixed alphabetic and numerical characters in sequence (Appendix B). Preoperative and postoperative performances (at 48 h) were compared regarding time taken and errors. Lengths of hospital stay, adverse events, or patient withdrawals were recorded.

Data were summarized as means ± standard deviation, medians and ranges, or categorized in contingency tables. Hypothesis testing used two-tailed Student's *t*-test for parametric data and Wilcoxon's ranked sum test for nonparametric data. VRS scores over 48 h were analyzed with analysis of variance for repeated measures. Contingency tables were assessed using Fisher's exact test. Regression techniques were used to control for confounding variables not matched in each group. Significance level was taken as $\alpha = 0.05$. Based on previous work (6), 120 patients were required for 80% power to detect a 25% change in subjective analgesic scores. Data from withdrawn patients were included in the analysis. Analyses were performed using STATA 7 (STATA Corp, College Station, TX).

RESULTS

Fifty-six patients were randomized to the ketamine group and 64 to the control group. SAE scores were collected on 115 patients at 24 h and 109 patients at 48 h. Losses were from withdrawal of four ketamine patients and six control patients. SAE data at 48 h were missing from one patient in the control group. Patient demographic and surgical data were similar (Table 1), but the control group had more smokers (*P* = 0.02).

A larger proportion of patients in the ketamine group reported excellent analgesia (42%) than control patients (17%) during the 0–24 h period (Table 2). At 24 h, the ketamine group was 2.5 times more likely to

Table 2. Subjective Analgesia Efficacy (%) After Surgery

Subjective analgesia efficacy	Ketamine	Control	<i>P</i>
At 24 h			0.008
Excellent = 1	23 (42%)	10 (17%)	
Good = 2	21 (38%)	34 (57%)	
Satisfactory = 3	9 (16%)	8 (13%)	
Poor = 4	2 (4%)	8 (13%)	
Total, <i>n</i>	55 (100%)	60 (100%)	
At 48 h			0.7
Excellent = 1	18 (35%)	19 (33%)	
Good = 2	23 (44%)	22 (39%)	
Satisfactory = 3	10 (19%)	15 (26%)	
Poor = 4	1 (2%)	0 (0%)	
Very Poor = 5	0 (0%)	1 (2%)	
Total, <i>n</i>	52 (100%)	57 (100%)	

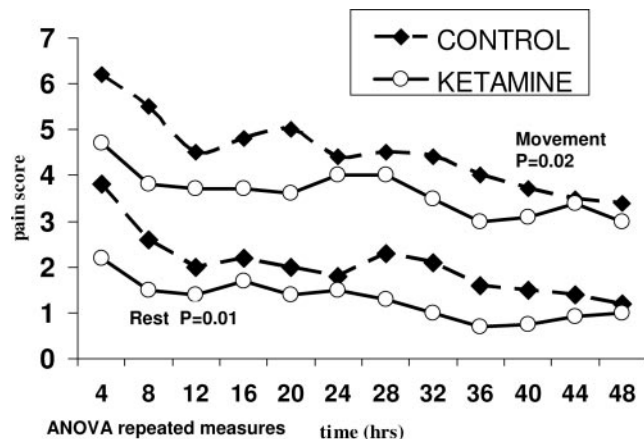


Figure 1. VRS pain scores 0–48 h.

have a SAE score of excellent than the control group (relative risk of excellent analgesia = 2.5 [95% CI 1.3–4.8]). The number needed to treat to obtain excellent analgesia by the addition of ketamine was four (95% CI 2.5–10). Fewer patients reported poor analgesia in the ketamine group (4%) than in the control (13%) at 24 h. The 24–48 h period showed no significant differences in SAE scores ($P = 0.7$) (Table 2).

Pain scores (VRS) were lower at rest ($P = 0.01$) and with movement ($P = 0.02$) over 48 h (Fig. 1). Median PCA morphine use was 46% greater in the control group (33.5 mg) than in the ketamine group (23 mg) during the 0–24 h period ($P = 0.003$) and 150% greater in the control group (30 mg) than the ketamine group (12 mg) in the 24–48 h period ($P = 0.001$). Analgesic interventions, defined as the need to increase the PCA morphine bolus or add a background morphine infusion, were more frequent in control patients (21 interventions) than ketamine patients (4 interventions) in the 0–24 h period ($P = 0.01$). The 24–48 h period had 9 interventions in control patients, 3 in ketamine patients ($P = 0.13$).

As study groups were not matched in terms of smoking status, the effect of possible confounding was explored by multiple logistic regression for ordinal SAE data, and multiple linear regression for morphine

Table 3. Postoperative Patient Data

	Ketamine	Control	<i>P</i>
Heart rate			
0–24 h	86 ± 12	84 ± 13	0.5
24–48 h	85 ± 11	84 ± 12	0.7
Systolic blood pressure			
0–24 h	133 ± 17	134 ± 18	0.8
24–48 h	136 ± 20	131 ± 17	0.1
Respiratory rate			
0–24 h	16 ± 2	16 ± 2	0.15
24–48 h	17 ± 1	17 ± 2	0.7
Sedation score			
0–24 h	0 (0–3)	1 (0–3)	0.03
24–48 h	0 (0–3)	0 (0–3)	0.08
Nausea score			
0–24 h	1 (0–2)	0 (0–2)	0.4
24–48 h	0 (0–2)	0 (0–2)	0.9
Antiemetic doses			
0–48 h	1 (0–8)	1 (0–8)	0.9

Values are mean ± SD or median (range).

consumption. The effect of smoking status was small, and not statistically significant, for both outcomes. For the 0–24 h period, the odds ratio of “excellent” analgesia (SAE score = 1) compared with “not excellent” (SAE score = 2–5) decreased from 3.8 to 3.5 after adjustment for smoking ($P = 0.4$) and from 1.1 to 1 in the 24–48 h period ($P = 0.3$).

Median sedation scores were lower in the ketamine group during the 0–24 h period ($P = 0.03$) but identical in the 24–48 h period ($P = 0.8$) (Table 3). There were no significant group differences in physiological variables, nausea score, or antiemetic administration (Table 3). Psychomotor, sleep disturbance, and Trail Making performance were similar (Table 4). Eleven patients (median age 73) experienced brief nondisturbing hallucinations, but were not withdrawn as they remained oriented. Such events were not significantly increased in the ketamine group. Three patients, all in the ketamine group, had disturbing hallucinations/confusion and were withdrawn. A further ketamine group patient was withdrawn because of uncontrolled pain. Control group withdrawals were due to uncontrolled pain (four patients) and respiratory depression (two patients). There were no deaths during the data collection period.

DISCUSSION

The addition of a small-dose ketamine infusion to tramadol resulted in superior analgesia, significant morphine-sparing, less sedation, and reduced need for physician intervention to manage pain after major abdominal surgery. The benefit from ketamine was evident throughout the 48-h study period but greatest in the first 24 h. There were similar neurocognitive side effects in the two study groups, although a few ketamine group patients were withdrawn because of disturbing hallucinations.

Overall pain scores were low, even though most patients had upper abdominal incisions. The study

Table 4. Psychomotor and Sleep Disturbance

	Ketamine	Control	<i>P</i>
Trail Making Test time (s)			
Preoperative (pre-admission clinic)	90 (35–300)	100 (40–240)	0.3
Postoperative (48 h)	101 (34–300)	115 (28–413)	0.7
Trail Making Test errors			
Preoperative (pre-admission clinic)	0 (0–5)	0 (0–4)	
Postoperative (48 h)	1 (0–6)	1 (0–8)	
Vivid dreaming: Yes/No			
0–48 h	19/36 (35%)	19/41 (32%)	0.8
Hallucinations			
Nondisturbing	6 (10.7%)	5 (7.8%)	
Disturbing (patient withdrawn)	3 (5.4%)	0 (0%)	
Sleep quality score ≥ 3 (sleep same or better than usual)			
0–24 h	26 (47%)	30 (50%)	0.5
24–48 h	27 (52%)	28 (50%)	0.6

Values are median (range) or proportion (%).

design achieved low pain scores, as patients with resting VRS >4 were assessed by pain physicians and the PCA morphine increased. Significantly reduced needs for such interventions in ketamine patients could be considered a surrogate marker for increased analgesic efficacy. Our study design was based on analgesic trials after laparotomy that also reported low pain scores (6,9), although combining ketamine and tramadol achieved better scores than morphine/ketamine (9) or morphine/tramadol (6).

Perioperative ketamine for acute postoperative pain has been recently reviewed (1,4,5). Elia and Tramer (4) concluded that, despite many published trials, the clinical relevance of adding ketamine for postoperative analgesia remained unclear. Reported pain score reductions were modest, with a weighted mean difference on the Visual Analog Scale of 0.35 cm at 24 h. Our study found similar modest pain score reductions, but the clinical relevance was clearer, as significantly more ketamine patients rated analgesia as excellent, suggesting that these modest reductions in pain were clinically meaningful during the 0–24 h period.

Similar SAE scores during the 24–48 h period suggested that lower pain scores and morphine use had less clinical meaning. The number of control group patients with excellent analgesia almost doubled during that time. Tramadol infusions as an adjunct to morphine PCA gave the best SAE scores and greatest morphine-sparing in the 24–48 h period, possibly from accumulation of active tramadol metabolites (6). This may also have blurred the SAE differences between groups during the same period in our study. Ketamine plasma levels may also have been relevant, as Owen et al. (10) found that fixed infusion rates of ketamine did not achieve constant levels in all patients, with 11/30 patients having decreasing levels with infusions running for 24 h (10). Our ketamine infusion rate was chosen, as similar rates were analgesic and opioid-sparing without adverse cardiovascular or psychomimetic effects (11,12). Tramadol infusion rates were based on efficacy shown in previous work (6).

Single ketamine doses during surgery achieved reduced pain and opioid consumption for hours longer than ketamine's expected pharmacological duration (13–15). It may therefore be questioned whether the ketamine infusion for 48 h in our study was necessary. However, prolonged analgesic benefit from single-dose ketamine was not shown after visceral surgery (16), so it would appear necessary to continue ketamine postoperatively in this patient group.

Lower pain scores in the ketamine group should be interpreted together with the significant morphine-sparing effect. Reduced morphine consumption may relate to the direct analgesic actions of ketamine mediated via cholinergic, μ , and monoaminergic mechanisms (2). Morphine reductions may also relate to prevention by ketamine of the linked phenomena of opioid-induced hyperalgesia and acute opioid tolerance (17). Joly et al. (17) showed that that PCA morphine requirements were higher after major surgery if large-dose remifentanyl had been given compared with small-dose remifentanyl, but least if large-dose remifentanyl was combined with ketamine. Hyperalgesia and allodynia adjacent to the surgical wound was also greater in the large-dose remifentanyl group. Ketamine infusion rates similar to ours have resulted in a significant reduction in hyperalgesia and morphine consumption (12).

Unlugenc et al. (7) showed, in a small trial, that ketamine-tramadol combinations achieved limited improvement in early postoperative analgesia compared with tramadol alone. Only 22 patients received ketamine in that study, and thus, the power was probably insufficient to detect the greater benefits we found. Patients received a tramadol infusion double that of ours and a smaller-dose ketamine infusion supplemented by patient-initiated boluses. Benefits from ketamine may have been blurred by larger tramadol doses, and studies indicate that PCA ketamine has lower efficacy than ketamine given by continuous infusion (1). Ketamine trials have frequently been small and Elia and Tramer. (4) reported the median number of subjects receiving ketamine in trials was only 25.

Less postoperative sedation in the ketamine group suggested the control group's higher morphine use impaired consciousness. Similar findings were reported in patients with morphine-resistant postoperative pain, where ketamine/morphine boluses resulted in less sedation and better analgesia than morphine boluses alone (15). Trials of ketamine as adjuncts to opioid analgesia have not generally shown sedation differences (1). Reduction of other opioid side effects was not shown in our trial, despite significant morphine-sparing. Morphine reductions may have been negated by tramadol or insufficient to affect postoperative nausea and vomiting rates. Reduced postoperative nausea and vomiting through morphine-sparing by ketamine was reported by one review (5), but another quantitative review did not find reduced opioid-related adverse effects (4). Sensitive tools to systematically evaluate opioid adverse effects, such as the opioid-related distress scale, have been proposed for further investigation (18).

Approximately 1/3 of patients in both groups experienced vivid dreaming. Similar rates were reported comparing PCA morphine/ketamine with PCA morphine alone after major surgery (9). Reeves et al. (9) reported a 23% hallucination rate when administering morphine PCA after major surgery and a 33% rate when ketamine was added. Our hallucination rate was considerably less, even though our study population was more elderly. Morphine use in the Reeves et al. study was more than double that of our study, which included tramadol. Tramadol may result in less psychomotor disturbance in the elderly than morphine (19). The Trail Making Test (Part B) times indicated no significant group differences in postoperative cognition.

A drawback of our study was the requirement of two infusion devices to administer ketamine and tramadol in addition to the morphine PCA device. Patients were hospitalized in standard surgical wards with pumps and lines identified by colored labels. No administration errors occurred. Combining ketamine and tramadol in the same fluid would simplify the technique, but pharmaceutical data supporting this were not available. The drugs were combined for 24 h in a previous study (7).

Despite randomization, more patients in the control group were smokers, requiring further statistical analyses to determine if smoking was a confounding effects. Smoking increased postoperative analgesia requirements in some studies, perhaps through nicotine withdrawal, increased postoperative coughing and cross-tolerance, although the exact mechanisms were not known (20). Adjusted results were not significantly different from unadjusted.

In conclusion, a small-dose ketamine infusion was a useful adjunct to a tramadol infusion after major surgery, as patients reported significantly better opinions of their analgesic medicine at 24 h and were less sedated. Pain scores were lower in the ketamine group

for 48 h after surgery with a significant morphine-sparing effect.

APPENDIX A

Pain Score (4 hourly)

Verbal rating scale (VRS): 0 (no pain) to 10 (worst imaginable pain)

Sedation Score (0-4) (4 hourly)

0 = alert, 1 = mildly drowsy/easy to arouse, 2 = frequently drowsy/easy to arouse, 3 = somnolent/difficult to arouse, 4 = asleep

Subjective Assessment of Analgesic Efficacy (1-5) (Daily)

"How effective was your medication in relieving your pain over the last 24 h?"

1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, 5 = very poor

Sleep Quality (1-5) (Daily)

"What has been your quality of sleep during the past 24 h?"

1 = much better than usual, 2 = better than usual, 3 = same as usual, 4 = worse than usual, 5 = much worse than usual

Nausea Score (0-2) (Daily)

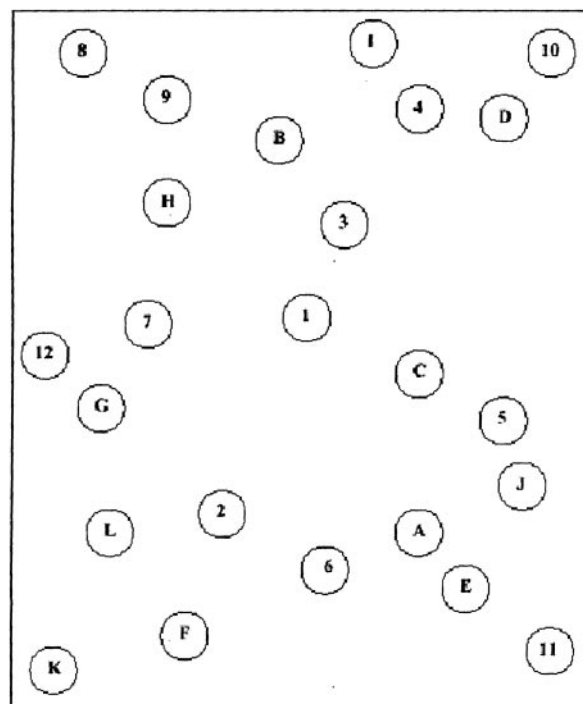
"How much nausea have you experienced over the last 24 h?"

0 = none, 1 = mild, 2 = severe

APPENDIX B

Trail Making (Part B)

Patient's Name: _____ Date: _____



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