

‘Balanced analgesia’ in the perioperative period: is there a place for ketamine?

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Abstract

We investigated whether intraoperative ‘subanesthetic doses’ of ketamine have a postoperative anti-hyperalgesic and an analgesic effect and which is the preferential route of administration, either systemic (intravenous, i.v.) or epidural. One hundred patients scheduled for rectal adenocarcinoma surgery under combined epidural/general anesthesia were included. Before skin incision all the patients received an epidural bolus followed by an infusion of continuous bupivacaine/sufentanil/clonidine mixture. They were randomly assigned to receive no ketamine (group 1), i.v. ketamine at the bolus dose of 0.25 mg/kg followed by an infusion of 0.125 mg/kg per h (group 2), 0.5 mg/kg and 0.25 mg/kg per h (group 3), epidural ketamine 0.25 mg/kg and 0.125 mg/kg per h (group 4), or 0.5 mg/kg and 0.25 mg/kg per h (group 5). All i.v. and epidural analgesics were stopped at the end of surgery and patients were connected to an i.v. morphine patient-controlled analgesia (PCA) device. Short-term postoperative analgesia (72 h) was assessed by pain visual analog scale scores at rest, cough, and movements as well as by PCA requirements. Wound mechanical hyperalgesia was evaluated and residual pain was assessed by asking the patients at 2 weeks, and 1, 6, and 12 months. The area of hyperalgesia and morphine PCA requirements were significantly reduced in group 3. These patients reported significantly less residual pain until the sixth postoperative month. These observations support the theory that subanesthetic doses of i.v. ketamine (0.5 mg/kg bolus followed by 0.25 mg/kg per h) given during anesthesia reduce wound hyperalgesia and are a useful adjuvant in perioperative balanced analgesia. Moreover, they show that the systemic route clearly is the preferential route. © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

‘Balanced analgesia’ consists of administration of analgesics acting on different systems to alleviate perioperative pain. Experimental studies clearly indicate that several systems are involved in the modulation of pain perception (Woolf, 1991). Moreover, drugs association allows reliable analgesia with lower dose of each component. Hence, the incidence of side effects can be reduced. For the aforementioned reasons, opiates, non-steroidal anti-inflammatory drugs, local anesthetics, and α_2 -adrenoceptor agonists are currently associated with the management of perioperative pain (Kehlet et al., 1999).

Recently, excitatory neurotransmitters (acting through *N*-methyl-D-aspartate (NMDA) receptor) have been incriminated in the development and maintenance of pathologic pain states after tissue injuries (mainly hyperalgesia and allo-

dynia) (Wilcox, 1991). This observation prompted the evaluation of NMDA receptor antagonists in various models of pain. In clinical practice, the anesthetic ketamine represents one of the few available NMDA antagonists (Lodge and Johnson, 1990). The drug also possesses some analgesic properties unrelated to an NMDA receptor binding. Ketamine activates the monoaminergic descending inhibitory system (Pekoe and Smith, 1982). This is a major system involved in the modulation of nociceptive processes, which is usually activated by systemic opiates and mimicked by α_2 -adrenoceptor agonists administration. In the present study, we investigated first whether ketamine has a specific effect on NMDA-related postoperative hyperalgesia using the methodology described by Stubhaug et al. (1997) and whether this drug could represent an efficient constituent of ‘balanced analgesia’. In addition, we intended to determine its preferential route of administration, either systemic or epidural.

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2. Methods

2.1. Patients

Adult patients, 55–75 years old, undergoing curative surgical resection of rectal adenocarcinoma (xypho-pubic incision) were considered. Severe hepatic, renal, cardiovascular, or psychological disorders, alcoholism or an inability to understand the study protocol were exclusion criteria. Patients were classified as American Society of Anesthesiologists (ASA) physical status I, II or III.

The study protocol received the approval of the human-subjects ethical committee of the Catholic University of Louvain and all patients provided written informed consent.

2.1.1. Presurgical education

The day before surgery, patients were taught how to use the visual analog scale (VAS) and the patient-controlled analgesia (PCA) pump as well. They were specifically instructed to self deliver analgesia at any time they began to feel pain. They received instructions to answer the postoperative pain questionnaire. They completed baseline psychometric evaluation. Information was given on the measures made by using the von Frey hairs.

Each patient was premedicated with lormetazepam 1 mg sublingual at 12 h before and approximately 1 h before surgery. Before anesthesia, an epidural catheter was inserted in all the patients at the T8–9 vertebral interspace. All the patients, in any group considered, received an epidural bolus of bupivacaine 0.5%, plus epinephrine 1/200 000 5–7 ml with sufentanil 2.5 µg and clonidine 1 µg/kg. This was immediately followed by an infusion of bupivacaine 0.125% with sufentanil 0.75 µg/h and clonidine 0.2 µg/kg per h at a rate of 4–5 ml/h. This epidural infusion was stopped at the end of surgery.

All patients received general intravenous (i.v.) anesthesia with propofol (3 mg/kg per h) and an oxygen/air mixture (fiO₂ 40%). Tracheal intubation was performed under propofol (±1.5 mg/kg), xylocaine 1 mg/kg, alfentanil 0.5 mg and atracurium 0.5 mg/kg. During the surgical procedure, additional boluses of propofol (0.5 mg/kg) were allowed to maintain a bispectral index between 55 and 65.

2.1.2. Patient randomization and intraoperative analgesia

According to a computer-generated table of random number assignments, each patient was assigned to one of five double-blinded groups. All patients received both i.v. and epidural infusions of either study medications or saline control. During surgery, intraoperative analgesia was achieved by the epidural bupivacaine/sufentanil/clonidine and by the ketamine or saline infusions. Both epidural infusion and ketamine were started ±30 min before skin incision and discontinued at the end of the surgical procedure. In case of inadequate intraoperative analgesia (more than 20% increase in systolic arterial blood pressure or heart rate occurring concomitantly with surgical noxious stimulation),

an additional bolus dose of i.v. alfentanil (0.5 mg) was given.

All studied solutions were prepared by an anesthesiologist who was not involved in the patient's care. The patient and the anesthesiologist who delivered anesthesia and evaluated analgesia also were blinded to the study solutions. The intraoperative discovery of an extended tumor resulted in the patient's exclusion. Finally, the correct placement of the epidural catheter was confirmed after the recovery by evaluating the metameric levels of thermoanalgesia using an ether swap.

2.2. Assessment of outcomes

After recovery of awareness, patients were connected to an i.v. PCA pump set to deliver 1.5 mg of morphine per demand with a 7 min lockout time and a maximum allowed dose of 30 mg per 4 h.

2.2.1. Early postoperative analgesia

Early postoperative analgesia was assessed using the following parameters.

- The cumulative number of met and unmet PCA morphine demands at 2, 6, 12, 24, 36, and 48 h.
- The pain VAS scores at rest, at cough, and at mobilization assessed by a blinded observer at 15 min and 2, 6, 12, 24, 36, and 48 h.
- The area of hyperalgesia for punctate mechanical stimuli around the surgical incision was measured at 24, 48, and 72 h according to the methods described by Stubhaug et al. (1997). Stimulation with a von Frey hair (396 mN) was started from outside the hyperalgesic area where no pain sensation was experienced toward the incision until the patient reported a distinct change in perception. The first point where a 'painful', 'sore', or 'sharper' feeling appeared was marked, and the distance to the incision was measured. If no change in sensation appeared, stimulation stopped at 0.5 cm from the incision. The area of hyperalgesia was determined by testing along radial lines at a distance of 5 cm around the abdominal incision. The observations were translated on graph paper and the surface area was calculated.
- At 48 h, patients evaluated the global quality of their early postoperative analgesia using a categorical scale (3, excellent; 2, good; 1, less than expected).

2.2.2. Residual pain

The incidence and importance of postoperative residual pain was evaluated at 2 weeks, 1 month, 6 months and 1 year after surgery. Patients were asked to answer the following questions.

1. Do you feel any pain at the scar area?
If yes: do you take medication to alleviate it?
If yes: do you take analgesic medications everyday?

And which one?

Do you take analgesic medications occasionally (at least three times per week)? And which one?

If no: do you feel particular sensations from the scar area?

Itching, burning, sensibility...

2. Do you feel pain at any other place?

If yes: where? Do you take analgesic medications?

3. Which unpleasant manifestations have you experienced since your operation?

This inquiry was performed by phone and confirmed by mail.

2.2.3. Side effects

Perioperative complications were recorded (e.g. hypotension, nausea). Particular attention was paid to detect both disturbing emergence reactions (e.g. hallucinations or bad dreams) and impairment in cognitive function during the early postoperative period. The Trail-Making test, which is a sensitive psychometric indicator of brain dysfunction, was used. This test involves two parts, A and B, and provides a measure of visual conceptual abilities and visuo-motor tracking (Spreeen and Benton, 1965). Part A requires the subject to connect in sequence 25 numbered circles located randomly on a page (i.e. 1-2-3...25). Part B requires the subject to connect the same number of circles numbered 1–13 with the remaining letters A–L by alternating between the two sequences (i.e. 1-A-2-B-3-C...). The time necessary to perform the test is taken into account. Trail-Making A and B were performed the day before surgery and at 2, 4, 24, 48, and 72 h after tracheal extubation.

2.3. Statistical analysis

Statistical analysis was performed with Statistica for Windows (version 5; Statsoft, Tulsa, OK). Statistical power calculations ($\alpha = 5\%$, $\beta = 10\%$) based on a pilot study suggested that a group size of 20 should detect a difference of at least 15 cm^2 in the surface of hyperalgesia. Parametric data (demographic data, time elapsed before first analgesic requirement, cumulative analgesic demands, morphine consumption, surface of hyperalgesia, Trail-Making tests) were analyzed using analysis of variance (ANOVA) and ANOVA for repeated measures. The normal distribution of the data was assessed according to the

Kolmogorov–Smirnov test. Post-hoc comparisons were made using the Tukey HSD test. Analysis of non-parametric data (VAS, satisfaction scores) was conducted with Kruskal–Wallis one-way ANOVA on ranks. A comparison of the observed proportions was performed using χ^2 analysis and the Fisher exact test with Yates' correction if appropriate. Results are expressed as the mean $\pm$ SD unless otherwise specified. A probability (P) value of less than 0.05 was considered to be statistically significant.

3. Results

The study protocol was proposed to 119 consecutive patients. Fifteen refused to participate and four were rejected because of an inability to perform the Trail-Making test. Two patients were excluded during surgery after discovery of widespread neoplastic disease. They were replaced by two new patients. All involved patients completed the postoperative pain survey except for eight who died before the conclusion of the observation period.

The demographic data are summarized in Table 1. Epidural catheter placement was successful at the first attempt in all cases. At the recovery, a correct level of thermoanalgesia was recorded in all the patients. Intraoperative additional anesthetic and analgesic requirements are presented in Table 2. Surgical procedures were uneventful; in particular, no patient required packed red blood cells transfusion.

3.1. Early postoperative analgesia

Pain VAS scores at rest, at cough and at mobilization were comparable in all the groups (Fig. 1). Cumulative satisfied analgesic requirements (Fig. 2) are significantly lower in patients in group 3 when compared to patients in groups 2, 4, and 5. At any time considered, the area of hyperalgesia was significantly reduced in group 3 when compared to groups 1 and 5 ($P < 0.05$) (Fig. 3). Patients' satisfaction scores are presented in Table 3.

3.2. Residual pain

Significantly less patients in group 3 suffered residual pain from the surgical area that required analgesic medications at 2 weeks, and 1 and 6 months ($P < 0.05$) (Fig. 4). In all the patients experiencing residual pain, paracetamol or

Table 1
Demographic data^a

Group	Female/male	Age (years)	Weight (kg)	Height (cm)	ASA (I/II/III)
1	10/10	67 $\pm$ 9	69 $\pm$ 11	167 $\pm$ 9	2/16/2
2	11/9	65 $\pm$ 10	73 $\pm$ 12	166 $\pm$ 8	1/15/4
3	8/12	69 $\pm$ 6	73 $\pm$ 12	168 $\pm$ 8	2/17/1
4	8/12	69 $\pm$ 6	74 $\pm$ 14	170 $\pm$ 9	2/16/2
5	10/10	67 $\pm$ 7	74 $\pm$ 13	167 $\pm$ 10	3/17/0

^a Values are the mean $\pm$ SD. No statistically significant differences were noted between the five groups.

Table 2

Intraoperative anesthetic and analgesic supplementations^a

Group	Anesthetic bolus supplementations ^b (n)	Analgesic bolus supplementations ^c (n)	Duration of anesthesia (min)
1	4 ± 3	0.3 ± 0.7	265 ± 71
2	3 ± 2	0.4 ± 0.8	251 ± 56
3	3 ± 2	0.2 ± 0.4	263 ± 58
4	4 ± 3	0.5 ± 0.9	269 ± 70
5	4 ± 2	0.4 ± 0.6	262 ± 80

^a Values are the mean ± SD. No statistically significant differences were noted between the five groups.

^b Propofol bolus 0.5 mg/kg.

^c Alfentanil bolus 0.5 mg.

occasionally paracetamol plus codeine (two patients) was sufficient to alleviate pain. At 6 months, resurgence of pain symptoms occurred in four patients (one in groups 1, 2, 4 and 5) and at 1 year in one other patient in group 5. In all these patients, a recurrence of the neoplastic disease was diagnosed. Ten patients reported low back pain during the observation period (three, two, two, two, and one patients in groups 1, 2, 3, 4 and 5, respectively). Eight of these patients reported an exacerbation of preoperative symptoms. Occasional medications or physiotherapy were required to alleviate this symptom. When considering patients' problems other than pain, it has to be noted that the most frequent ($\pm 20\%$ of patients per group) complaints were related to the surgical procedure itself (i.e. transit disturbances, or invalidating diarrheas). This was independent of the study groups.

3.3. Side effects

The incidence of postoperative nausea was low in all the groups considered. Approximately 90% of patients presented with less than five episodes of nausea or vomiting during the 72 first postoperative hours. None of the considered patients experienced nightmares or psychotomimetic effects, whereas one patient in group 5 presented with hallucinations on the fourth postoperative day. No intergroup differences were noted in the results of the psychometric evaluations. The time to complete Trail-Making A significantly increased during the first postoperative hours (from 47 ± 20 to 78 ± 14 s 2 h after recovery ($P < 0.05$)) and returned to baseline after 48 h (63 ± 20 s). The time to complete Trail-Making B followed the same pattern (from 106 ± 41 to 172 ± 33 s 2 hours after recovery ($P < 0.05$)). It returned to baseline only after 72 h (118 ± 44 s).

During the 1 year period, eight patients died from early postoperative pulmonary embolism (one patient in group 3), late myocardial death (>6 months) (one patient in group 1 and one patient in group 5), stroke (one patient in group 1), and recurrence of neoplastic disease (>6 months) (one patient in group 1, two patients in group 2, and one patient in group 4).

4. Discussion

Our results indicate that i.v. intraoperative ketamine at a subanesthetic dose significantly reduces mechanical hyperalgesia surrounding the surgical wound. It confirms the results obtained by others (Ilkjaer et al., 1996; Stubhaug et al., 1997). Moreover, i.v. ketamine improves postoperative analgesia by lowering early morphine consumption. It also

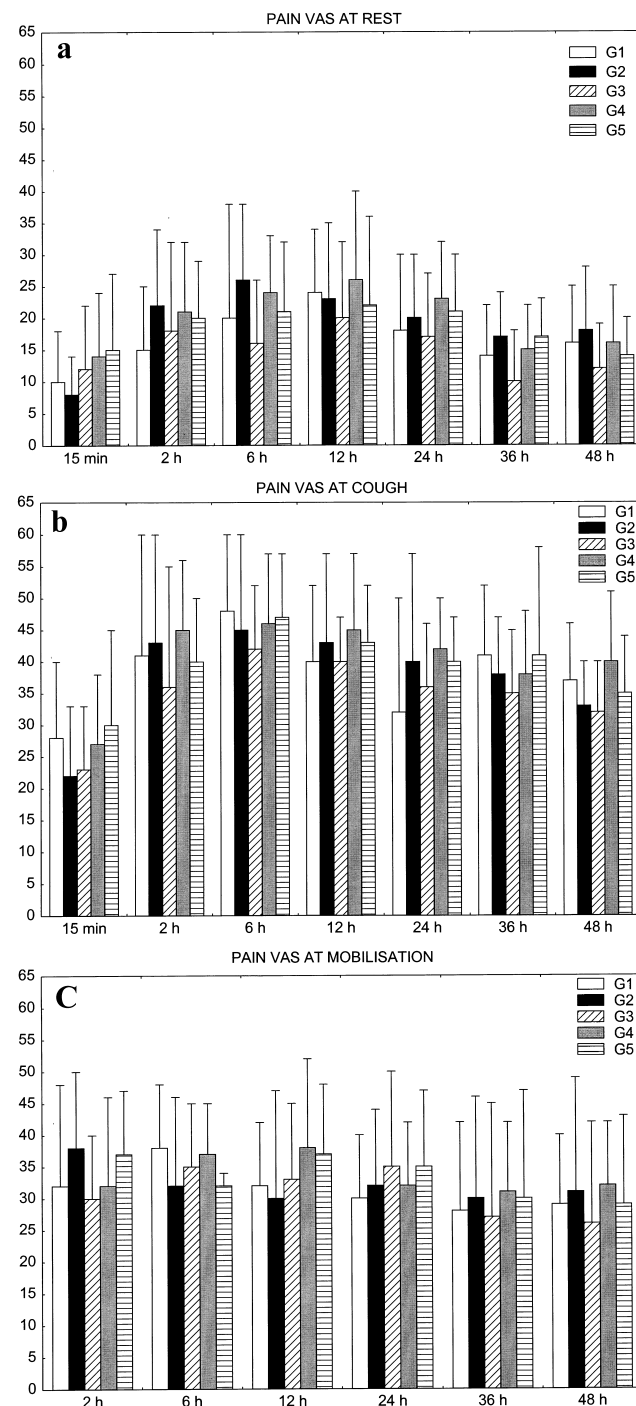


Fig. 1. Pain VAS scores at rest (a), at cough (b) and at mobilization (c). No statistically significant difference was noted at any time considered.

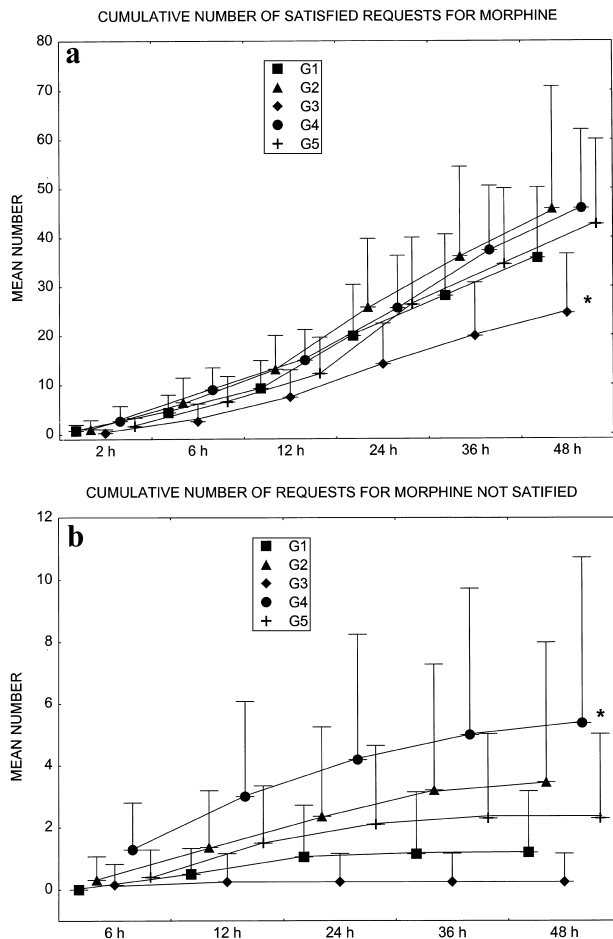


Fig. 2. Cumulative satisfied analgesic requirements (a) and between-dose demands (b). (a) *The number of satisfied analgesic requests was significantly lower in patients of group 3 when compared to patients in groups 2, 4, and 5. This difference is significant from the 24th postoperative hour ($P < 0.05$, ANOVA for repeated measures, post-hoc comparisons using the Tukey HSD test). (b) *The number of requests for morphine not satisfied is significantly superior in group 4 when compared to patients in groups 1, 3, and 5. This difference is significant from the 24th postoperative hour ($P < 0.05$, ANOVA for repeated measures, post-hoc comparisons using the Tukey HSD test).

diminishes the incidence of residual pain as expressed by analgesic requirements until the sixth postoperative month. These beneficial effects were not observed after epidural administration of ketamine.

The present study intended to answer whether ketamine can modulate postoperative hyperalgesia and hence has to be considered as a specific component of 'balanced analgesia'. In 1999, Schmid et al. published a review article summarizing all the publications from 1996 through December 1998 ($n = 22$) on the use and efficacy of subanesthetic doses of ketamine in the management of postoperative pain (Schmid et al., 1999). A subanesthetic dose of ketamine was defined as a bolus dose of less than 1 mg/kg via an i.v. or epidural route and as an infusion rate inferior to 20 $\mu\text{g/kg}$ per min; at these doses, ketamine possess analgesic effects in contrast with higher dose that produce psycho-

tomimetic side effects and 'dissociative anesthesia'. The conclusions provided by Schmid et al. were that "subanesthetic doses of ketamine in association with opiates and/or local anesthetics significantly improve pain scores, reduce the requirements for rescue medications, and when considered, the area of hyperalgesia surrounding the surgical wound".

According to these authors, more information, however, was mandatory concerning the best dose, the preferential

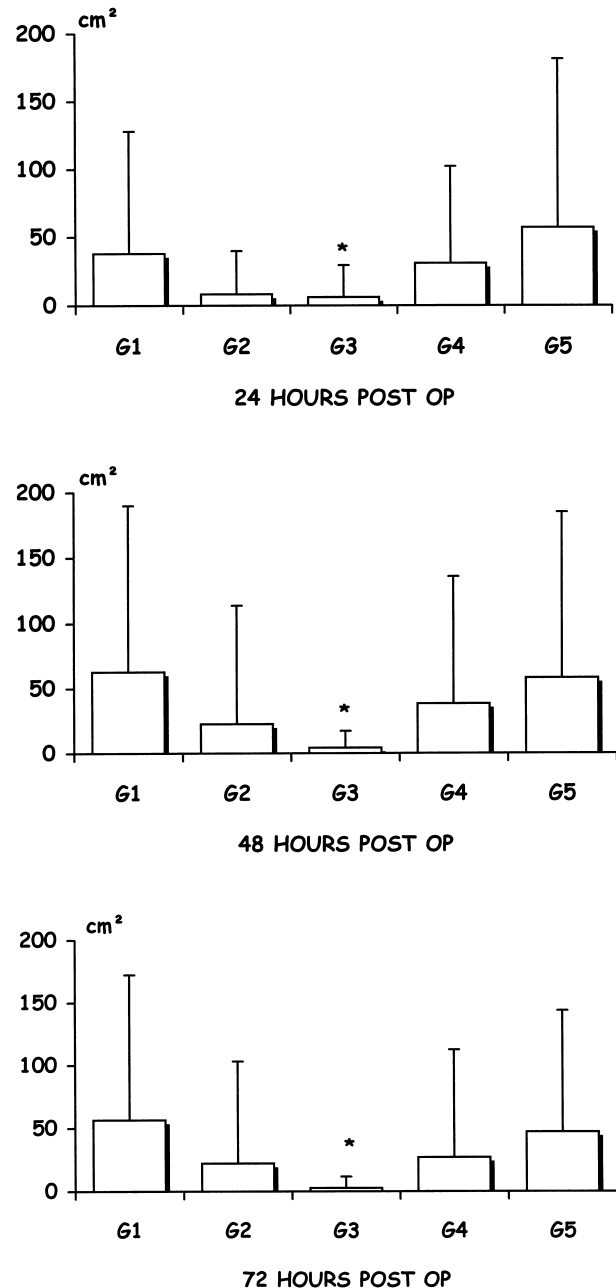


Fig. 3. Area of hyperalgesia measured using the von Frey hair after 24, 48, and 72 h. At any time considered, the area of hyperalgesia is significantly reduced in group 3 when compared to groups 1 and 5 ($P < 0.05$, ANOVA for repeated measures, post-hoc comparisons using the Tukey HSD test).

Table 3
Patients' evaluation of their postoperative analgesia^a

Group	Excellent (%)	Good (%)	Less than expected (%)
1	25	70	5
2	15	75	10
3	25	70	5
4	10	75	15
5	20	60	20

^a No statistically significant differences were noted between the five groups.

route of administration and the long-term effect on residual pain.

Our results report a significant improvement of postoperative analgesia in patients having received the highest tested dose among the subanesthetic doses of ketamine.

Moreover, this beneficial effect was only obtained after systemic administration, indicating that neuraxial administration is not the route of choice. This contrasts with other clinical studies that reported a significant effect after epidural administration (Wong et al., 1997; Choe et al., 1997; Chia et al., 1998). So, how can we explain this apparent discrepancy. The analgesic properties of ketamine have been known for a long time (Sadove et al., 1971) but the precise mechanisms are still unclear. Ketamine can act on several receptor systems such as opioidergic (μ , δ , and κ) (Smith et al., 1980; Finck and Ngai, 1982; Husveit et al., 1995) and cholinergic (muscarinic and nicotinic) (Husveit et al., 1995; Scheller et al., 1996), involves the monoaminergic system (Pekoe and Smith, 1982), and even shows local anesthetic effects by blockade of the sodium channels (Tung and Yaksh, 1981). All these interactions probably mediate analgesic effects not specifically related to the

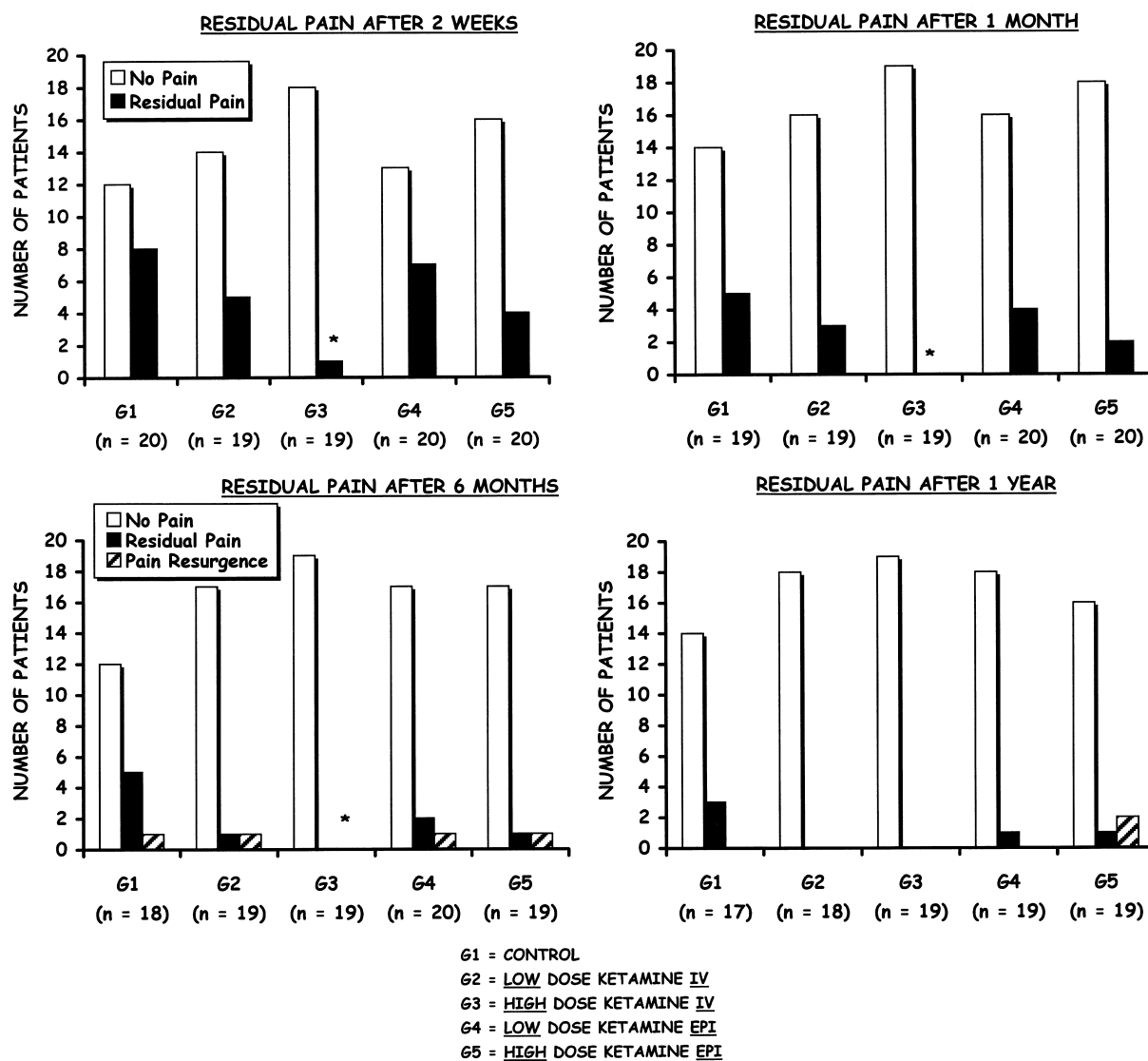


Fig. 4. Number of patients requiring chronic or occasional analgesic medications at 2 weeks, 1 and 6 months, and 1 year. Patients in group 3 required significantly less analgesic medications at 2 weeks, and 1 and 6 months than patients in the control group (group 1) ($P < 0.05$).

NMDA system and contribute to the alleviation of postoperative pain after epidural administration (Wong et al., 1997; Choe et al., 1997; Chia et al., 1998). Recently much attention has been paid to ketamine because of a non-competitive antagonism at the NMDA receptors, a system clearly involved in the development and maintenance of secondary hyperalgesia after tissue injury (Wilcox, 1991). Accordingly, ketamine may possess a 'specific' anti-hyperalgesic effect. An animal study by Kawamata et al. (2000) helps to discriminate between these two effects. The authors measured the effects of intraperitoneal or intrathecal ketamine on paw withdrawal latencies to heat stimulus in rats with or without paw inflammation. Involvement of the monoaminergic system was assessed by specific antagonist administration and cerebrospinal fluid microdialysis techniques. In the absence of inflammatory reaction, ketamine produces antinociceptive effects through an activation of the monoaminergic descending inhibitory system. This effect occurs only after systemic administration. In our study, however, a supraspinal effect on the monoaminergic descending inhibitory system cannot account for the observed difference between systemic and perimedullar administration since all the patients have received the α_2 -adrenergic agonist clonidine, a drug that mimics the activation of this inhibitory system. That is not the case in the epidural studies published by others (Wong et al., 1997; Choe et al., 1997; Chia et al., 1998) where α_2 -adrenergic agonist was not co-administered and where no comparison was made between systemic and epidural routes. Further, ketamine resorption from the epidural space into the systemic circulation is rapid (Pedraz et al., 1987), and hence a supraspinal effect cannot be ruled out in those studies. In Kawamata's rats presenting with peripheral inflammation, however, the antinociceptive effects of ketamine are clearly independent of the monoaminergic system and may be ascribed to a specific anti-NMDA effect. Further, in this situation, antinociception occurs independently of the route of administration.

The analgesic benefits that we observed in our patients are most likely related to such a 'specific' anti-hyperalgesic effect, but surprisingly they become manifest only after systemic administration. Why was epidural ketamine inefficient in the present study? Several explanations could be proposed. First, at the spinal level, NMDA receptors play an important role in the processing of pain perception. Particularly, these receptors prolong and amplify the nociceptive response (wind-up phenomenon) (Dickenson, 1995). All our patients received an epidural block with local anesthetics, opioids and α_2 -adrenoceptor agonists before and during the surgical procedure. This block may have prevented the action of epidural ketamine on spinal NMDA receptors. Ketamine induces a use-dependent, non-competitive blockade at the NMDA receptor that implies that the receptor channel has to be in an open state before that ketamine can bind to it. An epidural block which produces presynaptic inhibition of noxious afferents may have prevented the

NMDA receptor from being in this open state. Second, as suggested by Zahn and Brennan (1998), the role of spinal NMDA agonists in the pain consecutive to a surgical incision may be less important than in other experimental pain situations. These authors investigated the effects of spinal NMDA receptor antagonists on mechanical hyperalgesia in a model for postoperative pain and failed to demonstrate any significant spinal effect. Third, there exists a more central site for the anti-hyperalgesic action of ketamine, which is easily reached after systemic administration. Either intraperitoneal surgery activates noxious afferences (sensitive branches of the vagus nerve) which involves relay beyond the epidural block or a supra-spinal site is involved. In this regard two recent publications have pointed out the role of a supraspinal site, including the thalamus and rostral ventromedial medulla oblongata, in the maintenance of hyperalgesia associated with visceral inflammation (Kolhekar et al., 1997; Coutinho et al., 1998). Finally, ketamine directly interferes with the inflammatory reaction. Hill et al. (1998) demonstrated, *in vitro*, a potent inhibitory effect of ketamine on several proinflammatory cytokines. In the two later situations, systemic ketamine might be more efficient than epidural ketamine. A certain amount of drugs seems, however, to be required to reach this effect since the low systemic dose regimen used in our study was ineffective.

Finally, our study intended to evaluate the long-term benefits of perioperative ketamine administration. Chronic pain syndromes after abdominal surgery are not a rare phenomenon (Crombie et al., 1998). Boas et al. (1993) completed a 5 year study on 286 patients who underwent perineal resection for rectal cancer. In 11.5% of these patients, significant chronic pain syndromes, excluding a pain condition of immediate onset and related to inflammatory or healing problems, were noted. Most (70%) of these patients developed pain within weeks after surgery and the remaining 30% presented with pain several months later. This group with late onset pain died from known recurrence of adenocarcinoma in 80% of cases, whereas those with early pain had only a 26% tumor recurrence rate and symptoms of phantom anorectal pains in most cases. In our study, after 1 year of follow-up, only five patients (5%) experienced pain resurgence and two of them required pain clinic assistance because of invalidating pain. Tumor recurrence was the etiology of pain resurgence in all the patients and these findings reinforce the value of recurrent pain as a sensible indicator of tumor resurgence. None of the studied patients presented with phantom pain syndrome. This finding was independent of ketamine administration and may indicate a positive effect of preemptive analgesia as applied in our protocol. Our results also indicate that systemic ketamine significantly reduces the incidence of benign persistent residual pain. Whether this is a direct consequence of the specific anti-hyperalgesic or anti-proinflammatory properties of ketamine has not been determined.

Concerning the incidence of side effects, and particularly psychotomimetic and impairment in cognitive function

effects, our results confirm the conclusions summarized by Schmid et al. (1999) that low dose ketamine does not appear to induce more bothersome side effects than opioids or other usual analgesics.

In conclusion, the present study indicates that a subanesthetic dose of ketamine (0.5 mg/kg bolus followed by an infusion of 0.25 mg/kg per h) is a useful adjuvant for the perioperative balanced analgesia. The systemic route, when compared to the epidural one, is the preferential route of administration.

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