# *Intraoperative Epidural Analgesia Combined with Ketamine Provides Effective Preventive Analgesia in Patients Undergoing Major Digestive Surgery*

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*Background:* As a broader definition of preemptive analgesia, preventive analgesia aims to prevent the sensitization of central nervous system, hence the development of pathologic pain after tissular injury. To demonstrate benefits from preventive treatment, objective measurement of postoperative pain such as wound hyperalgesia and persistent pain should be evaluated. The current study assessed the role and timing of epidural analgesia in this context.

*Methods:* In a randomized, double-blinded trial, 85 patients scheduled to undergo neoplastic colonic resection were included. All the patients received a thoracic epidural catheter, systemic ketamine at a antihyperalgesic dose, and general anesthesia. Continuous infusion of analgesics belonging to the same class was administered by either intravenous or epidural route before incision until 72 h after surgery. Patients were allocated to four groups to receive intraoperative intravenous lidocaine–sufentanil–clonidine or epidural bupivacaine–sufentanil–clonidine followed postoperatively by either intravenous (lidocaine–morphine–clonidine) or epidural (bupivacaine–sufentanil–clonidine) patient-controlled analgesia. Postoperative pain scores (visual analog scale), analgesic consumption, wound area of punctuate hyperalgesia, residual pain, and analgesics needed from 2 weeks until 12 months were recorded.

*Results:* Analgesic requirements, visual analog scale scores, and area of hyperalgesia were significantly higher in the intravenous treatment group (intravenous–intravenous), and more patients reported residual pain from 2 weeks until 1 yr (28%). Although postoperative pain measurements did not differ, postoperative epidural treatment (intravenous–epidural) was less effective to prevent residual pain at 1 yr (11%; *P* = 0.2 with intravenous–intravenous group) than intraoperative one (epidural–epidural and epidural–intravenous groups) (0%; *P* = 0.01 with intravenous–intravenous group).

*Conclusion:* Combined with an antihyperalgesic dose of ketamine, intraoperative epidural analgesia provides effective preventive analgesia after major digestive surgery.

DESPITE the drugs and techniques we have at our disposal and the simple nature of incisional pain, optimal

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pain management remains a challenge.[1] Because the intensity of early postoperative pain correlates with the development of residual pain after some types of surgery, perioperative pain management can greatly influence the long-term quality of life in patients.[2] Operations such as thoracotomy, breast surgery, hernia repair, and amputation are well known to cause chronic pain problems, but major digestive procedures have received less attention, although among patients attending a chronic pain clinic, surgery specifically contributed to the development of pain in the abdomen and anal, perineal, and genital areas.[3] In this context, the concept of *preemptive analgesia* developed several years ago deserves some comment.[4] As a broader definition of preemptive analgesia, *preventive analgesia* includes any perioperative analgesic regimen able to control pain-induced sensitization of the central nervous system, hence to decrease both the development and the persistence of pathologic pain.[5]

In a previous study, we demonstrated that a low dose of intravenous ketamine, an antihyperalgesic drug that modulates excitatory neurotransmission, significantly reduces both mechanical hyperalgesia around the wound and incidence of residual pain in patients undergoing large bowel resection.[6] However, the exact contribution of epidural analgesia to this particular outcome remains to be determined, because all of the patients benefited from an intraoperative epidural treatment. Various clinical trials have already considered the role of epidural analgesia in providing preemptive analgesia.[7] Results of these studies have been inconsistent when only considering short-term benefits such as a sparing effect on postoperative analgesic demands or a decrease in immediate pain scores.[7,8] Particularly, the timing of epidural analgesia (preincisional *vs.* at emergence from anesthesia) is not clear. Further, only a few trials have extended their research beyond the early postoperative period. In a review article, Møiniche *et al.*[7] then suggested further studies focusing on *protective analgesia*, *i.e.*, aimed at the prevention of central nervous system sensitization and taking into account both immediate and late postoperative pain.

The current prospective study was therefore designed to examine the role and timing of balanced epidural analgesia as preventive treatment after major digestive surgery. The patients were randomly assigned to receive, by either the intravenous or the epidural route, intraop-

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**Table 1. Study Groups**

| | Group 1, IV–IV (n = 20) | Group 2, IV–EPI (n = 20) | Group 3, EPI–EPI (n = 20) | Group 4, EPI–IV (n = 20) |
|---|---|---|---|---|
| Ketamine | 0.5 mg/kg + 0.25 mg · kg−1· h−1 | 0.5 mg/kg + 0.25 mg · kg−1· h−1 | 0.5 mg/kg + 0.25 mg · kg−1· h−1 | 0.5 mg/kg + 0.25 mg · kg−1· h−1 |
| Intraoperative analgesia | Intravenous | Intravenous | Epidural | Epidural |
| | *Lidocaine* | *Lidocaine* | *Bupivacaine* | *Bupivacaine* |
| Bolus | 2 mg/kg | 2 mg/kg | 7 ml, 0.5% | 7 ml, 0.5% |
| Infusion | 0.5 mg · kg−1· h−1 | 0.5 mg · kg−1· h−1 | 5 ml/h, 0.125% | 5 ml/h, 0.125% |
| | *Clonidine* | *Clonidine* | *Clonidine* | *Clonidine* |
| Bolus | 4 μg/kg | 4 μg/kg | 1 μg/kg | 1 μg/kg |
| Infusion | 1 μg · kg−1· h−1 | 1 μg · kg−1· h−1 | 0.5 μg · kg−1· h−1 | 0.5 μg · kg−1· h−1 |
| | *Sufentanil* | *Sufentanil* | *Sufentanil* | *Sufentanil* |
| Bolus | 0.1 μg/kg | 0.1 μg/kg | 0.03 μg/kg | 0.03 μg/kg |
| Infusion | 0.07 μg · kg−1· h−1 | 0.07 μg · kg−1· h−1 | 0.015 μg · kg−1· h−1 | 0.015 μg · kg−1· h−1 |
| Before recovery | — | Epidural bolus* | — | — |
| Postoperative analgesia | Intravenous | Epidural | Epidural | Intravenous |
| | *Lidocaine* | *Bupivacaine* | *Bupivacaine* | *Lidocaine* |
| Bolus per request | 7.5 mg | 5 ml, 0.0675% | 5 ml, 0.0675% | 7.5 mg |
| Infusion | — | 5 ml/h, 0.0675% | 5 ml/h, 0.0675% | — |
| | *Clonidine* | *Clonidine* | *Clonidine* | *Clonidine* |
| Bolus per request | 15 μg | 3.5 μg | 3.5 μg | 15 μg |
| Infusion | — | 3.5 μg/h | 3.5 μg/h | — |
| | *Morphine* | *Sufentanil* | *Sufentanil* | *Morphine* |
| Bolus per request | 1.3 mg | 0.05 μg | 0.05 μg | 1.3 mg |
| Infusion | — | 0.05 μg/h | 0.05 μg/h | — |

* Group 2 received an epidural bolus administered at the end of surgery after ending intravenous infusion: 7 ml bupivacaine, 0.5%; 1 μg/kg clonidine; and 0.03 μg/kg sufentanil.

EPI = epidural; IV = intravenous.

erative and postoperative balanced analgesia based on similar analgesic drug regimens (combination of local anesthetic, μ-opioid agonist, and $\alpha_2$-adrenergic agonist). To evaluate the preventive effect of epidural treatment, the study focused on the development of postoperative wound hyperalgesia and residual pain up to 1 yr after the procedure. Effectively, the degree of central nervous system sensitization is not reflected in clinical parameters commonly assessed, such as pain scores or postoperative analgesic need.[9] In contrast, the area of punctuate mechanical hyperalgesia developed around the incision can be used as an objective tool to evaluate the degree of central sensitization[10] and could perhaps predict patients who are likely to have persistent pain.[1]

## Materials and Methods

### Patients

The study included adult patients undergoing curative surgical resection of rectal adenocarcinoma (xiphopubic incision). Severe hepatic, renal, cardiovascular, or psychological disorders, preexisting pain syndrome, and/or analgesic treatment, alcoholism, or inability to understand the study protocol were exclusion criteria. Patients were classified as having American Society of Anesthesiologists physical status I, II, or III. The study protocol received the approval of the human subjects ethical committee of the Catholic University of Louvain

(Brussels, Belgium), and all patients provided written informed consent.

The day before surgery, patients were taught how to use the visual analog scale and the patient-controlled analgesia (PCA) devices. They were instructed to self deliver analgesia at any time they began to feel pain and received instructions to answer the postoperative pain questionnaire.

After premedication with 1 mg lormetazepam and before induction of anesthesia, a thoracic epidural catheter was inserted at eighth thoracic vertebral interspace in all patients. Tracheal intubation was performed during propofol, 2.5 μg sufentanil, and atracurium, and anesthesia maintenance was accomplished with propofol (3 mg · kg$^{-1}$ · h$^{-1}$) and oxygen–air mixture (fraction of inspired oxygen, 40%). During the surgical procedure, additional boluses of propofol (0.5 mg/kg) were allowed to maintain a Bispectral Index between 55 and 65.

**Patient Randomization and Intraoperative Analgesia.** According to a computer-generated table of random number assignments, each patient was assigned to one of four double-blinded groups. All patients received both intravenous and epidural infusions of either study medications or saline. Intravenous or epidural intraoperative analgesic infusions were started 30 min before skin incision. The different groups are presented in table 1. During surgery, analgesia was achieved by the fixed rate of either epidural bupivacaine–sufentanil–clonidine in-

fusion (groups 3 and 4, receiving intravenous saline infusion) or intravenous lidocaine–sufentanil–clonidine infusion (groups 1 and 2, receiving epidural saline infusion). All these infusions were stopped at the end of skin closure.

In all of the patients, an effective antihyperalgesic dose of ketamine as determined in our previous study[6] (0.5-mg/kg bolus followed by continuous infusion at $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started before skin incision and discontinued at the end of the procedure. In case of cardiocirculatory parameter variations consecutive to surgical noxious stimulation ($> 20\%$ increase in systolic arterial blood pressure and/or heart rate), an additional bolus dose of 2.5 $\mu$g intravenous sufentanil was given.

All of the analgesic solutions were prepared by an anesthesiologist who was not involved in the patients' care. In the epidural groups, this anesthesiologist confirmed the correct placement of the epidural catheter after recovery by evaluating the metameric levels of thermoanalgesia using an ether swab. Absence of thermoanalgesia level as well as intraoperative discovery of an extended tumor resulted in the patient's exclusion from the study. The same anesthesiologist removed the epidural catheter in patients who would benefit from postoperative intravenous PCA. We acknowledge that this fact represents a limitation of the study because it prevented a true double blinding in the postoperative period. For practical reasons, it was not possible to connect the patient with both intravenous PCA and patient-controlled epidural analgesia (PCEA) devices, which would have resulted in confusion and misuse of these devices, then causing a decrease in their efficacy, with poor pain relief and satisfaction for our patients. Notwithstanding, we can consider that the study remained double blinded because postoperative parameters were recorded by an anesthesiologist who was not aware of the intraoperative treatment administered to the patient (either effective epidural or intravenous injection), and the patients, who were using either postoperative intravenous PCA or PCEA, did not know which intraoperative treatment they had received.

**Postoperative Analgesia.** Immediately after recovery, the patients were connected to either an intravenous PCA device (groups 1 and 4) or a PCEA device (groups 2 and 3). Drugs delivered by the different devices are summarized in table 1. Intravenous PCA devices were set to deliver 0.75 ml solution per demand with a 7-min lockout time and a maximum allowed volume of 15 ml/4 h. Epidural PCEA devices were set to deliver a continuous infusion of 5 ml/h and a 5-ml bolus on request with a 40-min lockout time. Analgesic regimens were supplied during 72 h.

*Outcome Assessment*

**Early Postoperative Pain and Analgesia.** Early postoperative pain and analgesia were assessed using the
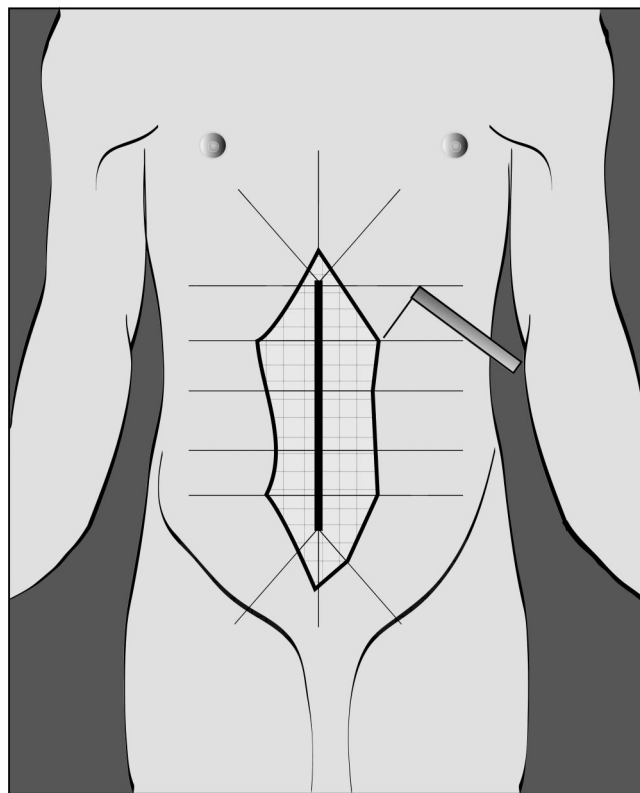


**Fig. 1. Schematic representation for the mapping of the area of punctuate mechanical hyperalgesia surrounding the surgical incision. Stimulation with von Frey filament (396 mN) started from the periphery toward the surgical incision following the testing trajectories and stopped when the patient reported a distinct change in perception.**

following parameters: cumulative number of met PCA or PCEA demands at 12, 24, 48, and 72 h and visual analog scale pain scores at rest, cough, and mobilization assessed by a blinded observer at 30, 60, 90, and 120 min and 24, 48, and 72 h.

The area of hyperalgesia for punctuate mechanical stimuli around the incision was measured at 24, 48, and 72 h according to the method described by Stubhaug.[10] 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 (fig. 1). The first point where a "painful," "sore," or "sharper" feeling occurred was marked, and the distance to the incision was measured. If no change in sensation occurred, the 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 incision, and all these observations were translated to graph paper to calculate the surface area. In the groups benefiting from postoperative epidural analgesia, the last measurement was performed 4 h after the discontinuation of epidural analgesic administration.

**Table 2. Demographic Data and Intraoperative Management**

|  | Group 1, IV–IV | Group 2, IV–EPI | Group 3, EPI–EPI | Group 4, EPI–IV |
|---|---|---|---|---|
| Age, yr | 53 ± 8 | 54 ± 8 | 55 ± 8 | 53 ± 10 |
| Female/male, n | 8/12 | 7/13 | 8/12 | 8/12 |
| Weight, kg | 68 ± 8 | 55 ± 8 | 70 ± 10 | 69 ± 10 |
| Height, cm | 172 ± 10 | 170 ± 10 | 169 ± 10 | 171 ± 9 |
| ASA, I/II/III | 4/15/1 | 4/15/1 | 3/15/2 | 3/16/1 |
| Duration of anesthesia, min | 272 ± 63 | 264 ± 58 | 273 ± 66 | 282 ± 74 |
| Anesthetic bolus supplements,* n | 5 ± 1 | 4 ± 2 | 3 ± 3 | 2 ± 2 |
| Analgesic bolus supplements,† n | 2.0 ± 1.2 | 1.4 ± 1.1 | 0.2 ± 0.5‡ | 0.1 ± 0.3‡ |

Values are presented as mean ± SD where appropriate.

* Propofol bolus of 0.5 mg/kg. † Sufentanil bolus of 2.5 $\mu$g. ‡ Significant difference ($P < 0.05$) with group 1.

ASA = American Society of Anesthesiologists physical status classification; EPI = epidural; IV = intravenous.

**Residual Pain.** The incidence and importance of postoperative residual pain was evaluated at 2 weeks and 1, 6, and 12 months after surgery by the following questions:

1. Do you feel any pain at the scar area? *If yes:* Do you take medication to alleviate it? Every day or occasionally (at least 2 times per week)? Which one(s)? *If no:* Do you have any particular sensations from the scar area? Itching, burning, sensitivity . . .
2. Do you feel pain at any other place? *If yes:* Where? Do you take analgesics?
3. Which unpleasant manifestations have you experienced since your operation?

This enquiry was performed by the research nurse with a phone call and was confirmed by mail.

**Side Effects of Treatments.** Perioperative complications such as hypotension, nausea or vomiting, and hallucinations or nightmares were recorded.

*Statistical Analysis*

Statistical analysis was performed with Statistica for Windows (version 5; Statsoft, Tulsa, OK). Statistical power calculations ($\alpha = 5\%$, $\beta = 10\%$), based on our first study[6] considering this class of patients, suggested that a group size of 20 should detect a difference of at least 15 cm$^2$ in the surface of hyperalgesia. Parametric data were analyzed using analysis of variance and analysis of variance 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 honest significant difference test. Nonparametric data (visual analog scale score, satisfaction scores) were conducted with Kruskal-Wallis one-way analysis of variance on ranks. Comparison of the observed proportions was performed using chi-square analysis with corrections for multiple groups. Results are expressed as mean ± SD or otherwise specified. A probability ($P$) value of less than 0.05 was considered to be statistically significant.

## Results

The study protocol was proposed to 85 consecutive patients during a 30-month period. One declined to participate, and one was excluded because of inability to understand the protocol. One was excluded during surgery after discovery of widespread neoplastic disease, and two other patients were excluded for postoperative early dislocation of epidural catheter (before 72-h follow-up). All involved patients completed the postoperative pain survey except for one who died of a cardiac arrest at home 2 months before the conclusion of the 1-yr observation period. The demographic data are summarized in table 2. Epidural catheter placement displayed a correct level of thermoanalgesia in all the patients after testing. Intraoperative additional anesthetic and analgesic requirements are presented in table 2. Surgical procedures were uneventful; particularly, no patient required packed erythrocyte transfusion.

**Early Postoperative Analgesia.** Pain visual analog scale scores at rest, cough, and mobilization are summarized in figure 2. Patients in group 1 (intravenous–intravenous) experienced significantly more severe pain than patients in the three other groups. Cumulative number of satisfied analgesic requirements was significantly higher in group 1 (intravenous–intravenous) than in the other groups (fig. 3).

**Hyperalgesia and Residual Pain.** At any given time, the area of punctuate hyperalgesia was larger in group 1 when compared with groups 2, 3, and 4 ($P < 0.05$; fig. 4). Significantly more patients in group 1 experienced residual pain from the surgical area that required analgesic medications at 2 weeks, 1 month, 6 months, and 1 yr (fig. 5). At 2 weeks, fewer patients in group 3 presented with pain than patients in group 1 (45 *vs.* 86%; $P = 0.02$). At 1 and 6 months, more patients in group 1 reported residual pain (62 and 48%; $P < 0.05$) than patients from all the other groups that did not differ. After 1 yr, 28% reported pain and 14% needed analgesics in group 1, whereas 11% had pain and 5% had taken medications in group 2 ($P = 0.2$). Patients in groups 3
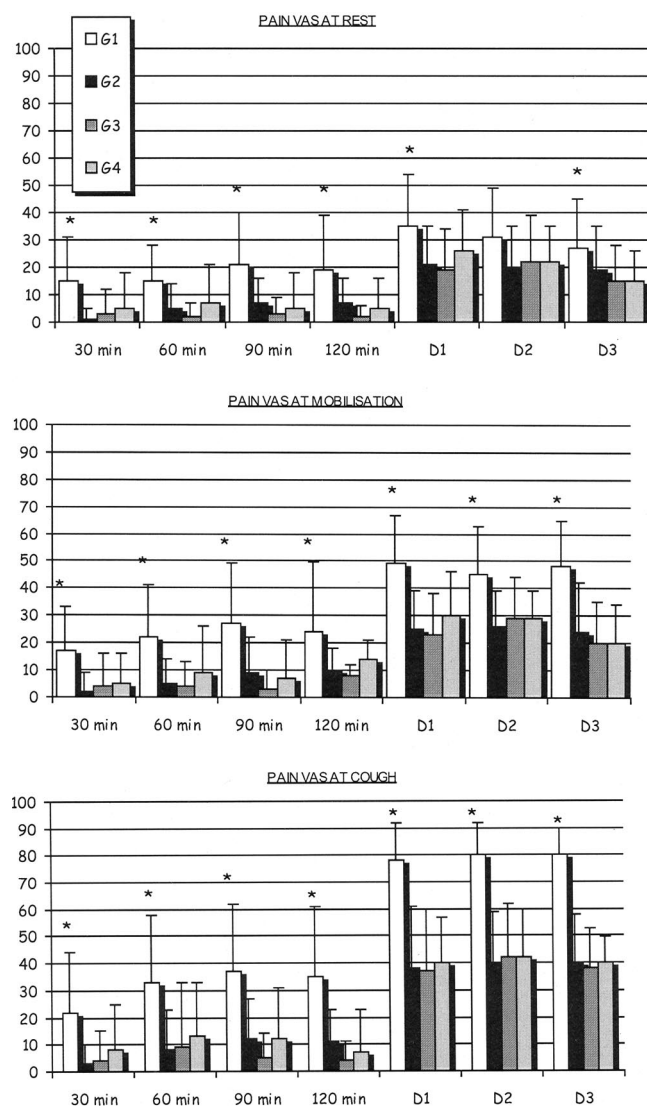
Fig. 2. Immediate postoperative visual analog scale (VAS) scores. Pain VAS scores from 0 (no pain) to 100 (maximal pain) at rest, at mobilization, and at cough. * P < 0.05 between group 1 (G1: intravenous–intravenous) and all the other groups (G2: intravenous–epidural; G3: epidural–epidural; G4: epidural–intravenous).
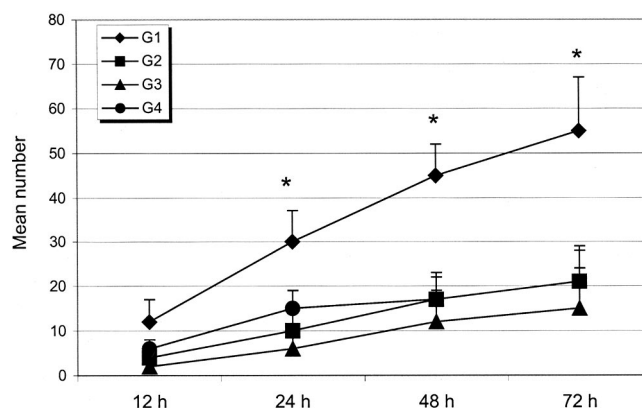


Fig. 3. Postoperative use for epidural and intravenous patient-controlled analgesia assessed as number of cumulative satisfied analgesic requirements. Cumulative satisfied analgesic requirements in postoperative epidural patient-controlled epidural analgesia groups (G2: intravenous–epidural; G3: epidural–epidural) and intravenous patient-controlled analgesia groups (G1: intravenous–intravenous; G4: epidural–intravenous). The number of satisfied analgesic requests was significantly higher, * P < 0.05 in patients of G1 when compared with patients in G2, G3, and G4. This difference was significant from the 24th postoperative hour.

in patients benefiting from epidural analgesia (group 2: 70%, group 3: 71%; P ≤ 0.05).

## Discussion

Our study demonstrates a clear benefit of continuous perioperative epidural analgesia as preventive treatment on the development of residual pain after major digestive surgery. Further, intraoperative use of epidural analgesia seems to provide a higher benefit than only postoperative use when we take into account the presence of residual pain at 1 yr after surgery (0 vs. 11%, respectively; P = 0.01 and P = 0.2 with the intravenous analgesic treatment group). Finally, this study confirms the superiority of an effective neuraxial block over an effective parenteral analgesia after major surgery, thus highlighting the major contribution of spinal sensitization in both short- and long-term incisional pain.

Until recently, most clinical trials have focused on whether epidural analgesia improved anesthetic outcomes, such as myocardial ischemia, venous thrombosis, or gastrointestinal function, rather than on analgesia.[11] A reduction of postoperative mortality and morbidity supports by itself a widespread use of epidural technique during the perioperative period, especially in critical patients.[12] For major gastrointestinal surgery, beneficial effects, such as enhanced functional exercise capacity and health-related quality of life at 6 weeks, have been demonstrated that rely on superior quality of pain relief provided by the epidural technique.[13] However, although it is now well known that the intensity of acute postoperative pain also correlates with the development of residual pain after some type of surgery,[2] the long-

and 4 were pain free (P < 0.05 with group 1). In patients experiencing residual pain, paracetamol plus codeine was sufficient to alleviate pain. At 1 yr, resurgence of pain symptoms occurred in 1 patient of group 2, who had a recurrence of the neoplastic disease.

Six patients (two in group 1, one in group 3, and three in group 4) reported the presence of back pain at the site of epidural placement that persisted between 2 and 6 months after the procedure.

**Side Effects.** The incidence of postoperative nausea was low in all the groups considered. None of the considered patients experienced nightmares or psychomimetic effects. Orthostatic hypotension at first mobilization was significantly lower in patients receiving intravenous analgesia (group 1: 30%, group 4: 45%) than
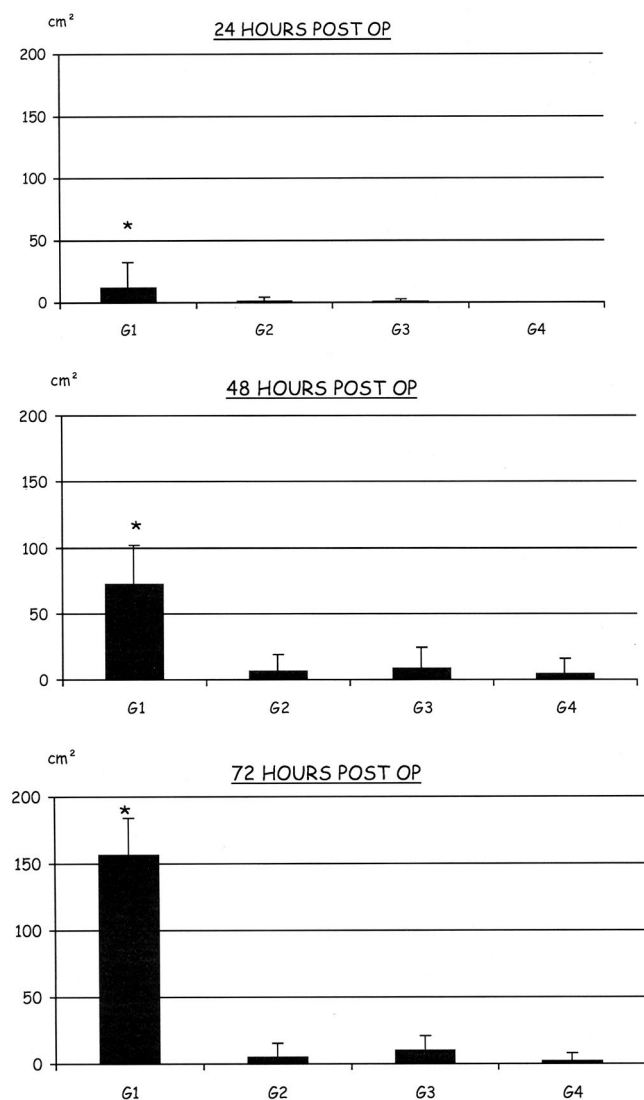
Fig. 4. Postoperative area of punctuate hyperalgesia around the wound. Area of hyperalgesia measured using the von Frey hair after 24, 48, and 72 h. At any time considered, the area of hyperalgesia was significantly higher, * *P* < 0.05 in group 1 (G1: intravenous–intravenous) when compared with groups 2, 3, and 4 (G2: intravenous–epidural; G3: epidural–epidural; G4: epidural–intravenous).

term benefits of perioperative analgesic techniques have not been extensively investigated after major surgical procedures. To our knowledge, only one study has used a similar design with four treatment groups. In this study by Norris *et al.*,[14] however, the use of intraoperative thoracic epidural analgesia did not offer an advantage in patients undergoing abdominal aortic surgery. All postoperative outcomes were similar between the groups, but only immediate postoperative pain scores were evaluated, not incisional hyperalgesia or long-term residual pain. However, our results differ from those of Norris *et al.* because we have found that both intraoperative and postoperative epidural blocks clearly reduce pain scores and analgesic requirement during the immediate postoperative period in comparison with parenteral analgesics.

One explanation for such a discrepancy might be related to the fact that Norris *et al.* used less aggressive epidural analgesia than we did, providing incomplete block of nociceptive inputs at the spinal level.

In contrast with the various published trials questioning the preemptive analgesic effect of epidural analgesia, few studies have evaluated its benefits in a broader context, *i.e.*, as preventive analgesia aimed to prevent postoperative pain persistence. Some of our results (*i.e.*, the comparison between all the epidural groups) support findings from others who did not show an overall improvement in early postoperative pain relief, assessed by pain scores and analgesics need, with initiation of epidural block before surgical incision or later (a definition of preemptive analgesia).[7,15] According to the studies of incisional pain performed in both an animal model[16] and human volunteers,[17] locoregional block before or after the incision is roughly equivalent to relieve spontaneous pain and primary hyperalgesia because incisional pain requires permanent ongoing afferent inputs generated from the wound. The peripheral nociceptive inputs from the injured site trigger hypersensitivity and central sensitization, which can lead to the development of persistent pain in some cases.[1,18] Mapping the area of punctuate hyperalgesia close to the wound allows an objective measurement of central sensitization. Besides, the administration of drugs with antihyperalgesic properties, *e.g.*, the clinically available glutamate receptor antagonist ketamine, significantly reduces punctuate hyperalgesia and suppresses central sensitization.[6,10] In the current study, where all the patients received ketamine as a antihyperalgesic regimen, the mapping of wound hyperalgesia unraveled the fact that either intraoperative or postoperative epidural analgesia significantly reduced central sensitization when compared with the intravenous analgesic regimen alone. That clearly indicates a preferential spinal site of action for the antihyperalgesic properties of epidural analgesia, in accord with neurophysiologic data pointing out the major role of the spinal cord in both integration and modulation of pain sensation.[18] Further, the spinal cord remains the preferential site of analgesic action for local anesthetics as well as for the $\alpha_2$-adrenoceptor agonist clonidine,[19] and regardless of whether a supraspinal effect cannot be ruled out for lipophilic $\mu$-agonist such as sufentanil because systemic resorption after epidural administration is fast and extensive, a major analgesic effect seems mediated at the spinal level.[20] Moreover, among the drugs we administered by the epidural route, clonidine, besides its analgesic action, possesses interesting spinal antihyperalgesic effects. Indeed, clonidine, spinal but not intravenous administration of which suppresses hyperalgesia induced by capsaicin injection in human volunteers,[21] binds to both $\alpha_1$- and $\alpha_2$-adrenergic receptors. Stimulation of $\alpha_2$ adrenoceptors reduces afferent release of glutamate, whereas through $\alpha_1$-adrenoceptor stimula-
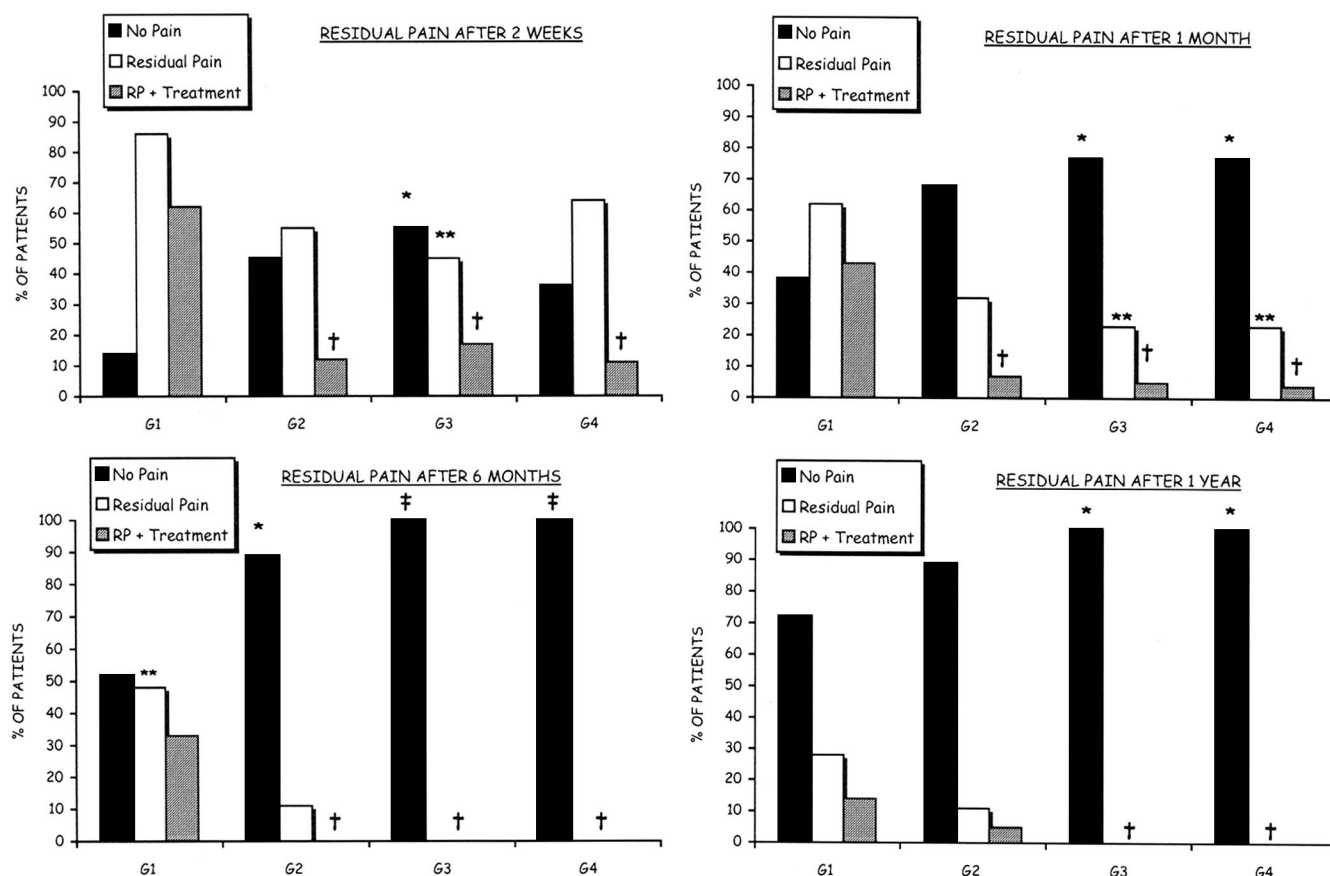
**Fig. 5. Postoperative residual pain. Number of patients presenting residual pain and requiring chronic or occasional analgesic medications at 2 weeks, 1 month, 6 months, and 1 yr. \*,\*\*,† $P < 0.05$, ‡ $P < 0.01$ with patients in group 1 (G1: intravenous–intravenous) regarding the following parameters: no pain, residual pain at incision site, and analgesics need. Other groups: G2: intravenous–epidural; G3: epidural–epidural; G4: epidural–intravenous. RP = residual pain.**

tion on inhibitory interneurons, clonidine provokes local release of γ-aminobutyric acid and glycine.[22] The use of balanced epidural analgesia involving a combination of drugs with analgesic and antihyperalgesic properties contributes to explain the benefits observed on postoperative pain relief and reduction of hyperalgesia close to the wound.

Although systemic administration of lidocaine is also effective to decrease mechanical hyperalgesia in some painful conditions and after skin incision in volunteers,[23] we did not find any significant effect after major digestive surgery. The antihyperalgesic effect of systemic local anesthetic could have been obscured by the concomitant administration of ketamine, or another possible explanation might be related to the low dosage of intravenous lidocaine we used ($0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$).

Our data are in accord with a recent study by Katz et al.,[24] where intraoperative epidural block, either preincisional or postincisional, was superior to no epidural treatment (another definition of preemptive analgesia involving a control group) in decreasing mechanical sensitization around the wound after laparotomy. However, the study of Katz et al. did not allow questioning of the idea that intraoperative and postoperative noxious in-

puts might have separate contributions to the process of central sensitization because postoperative analgesia was provided by systemic opioids in all of the groups. Further, epidural analgesia only resulted in short-term beneficial effects with less pain disability at 3 weeks but no more significant difference at 6 months after surgery.[15] Our results show that regardless of whether postoperative is as effective as intraoperative epidural analgesia to prevent the installation of mechanical hyperalgesia around the wound, an effective intraoperative neuraxial block is superior to reduce central sensitization after major surgery and hence the risk of residual pain.

Our results also are in accord with some of the few trials that have previously examined the impact of epidural block on long-lasting pain after surgery. Obata et al.[25] found lower pain scores and less residual pain at 6 months after thoracotomy when continuous epidural block was initiated intraoperatively instead of at the completion of surgery. Gottschalk et al.[26] also reported lower pain and more pain-free patients 9.5 weeks after prostatectomy in those who received a continuous intraoperative neuraxial block in comparison with no epidural block during the surgery. In both studies,[25,26] how-

ever, all of the patients benefited from an effective and aggressive postoperative epidural analgesia. In contrast, Ochroch *et al.*[27] did not find an impact of continuous intraoperative thoracic epidural analgesia on long-term pain and recovery after thoracotomy, as did Jensen and Andersen[28] on poststernotomy pain after cardiac surgery. One explanation might be related to the different doses and combinations of analgesic drugs used to block nociceptive afferent barrage to the spinal cord, as previously discussed.

Finally, none of the aforementioned trials[15,25–27] involved intravenous coadministration of ketamine. The intraoperative adjunction of this antihyperalgesic drug to an effective central block might have contributed to explain our results because the two treatments have combined actions in reducing central nervous system sensitization. Beyond antihyperalgesic properties exerted at the supraspinal level, as we demonstrated in a previous study,[6] ketamine also possess antiinflammatory effects that can modulate perioperative cytokine balance and pain.[29] When we compare the long-term effect of our preventive treatments on the same surgical procedure and using similar epidural and/or intravenous analgesic regimens, we found that, without intraoperative ketamine but with intraoperative epidural block and postoperative morphine PCA, 66% of patients were pain free at 6 months,[6] in comparison with 100% of patients who were pain free when intraoperative ketamine was combined with intraoperative epidural block,[6] as was the case in the current study.

In summary, chronic postsurgical pain is not rare, and even relatively low levels of residual pain can significantly affect social and physical function in patients. Because perioperative pain management influences surgical outcome and the possible development of persistent pain in some patients, particular attention should be paid to preventive analgesic techniques of analgesia. Although the current study was not designed to evaluate the incidence and severity of disability and pain after major abdominal procedures, we have demonstrated that epidural analgesia is additive to systemic intraoperative administration of an antihyperalgesic drug such as ketamine to reduce both early postoperative hyperalgesia and persistent postsurgical pain. Regardless of whether our study provides clinical evidence that both intraoperative and postoperative epidural analgesia allow prevention of the development of persistent pain after major digestive surgery, it also seems that intraoperative suppression of spinal sensitization through an effective epidural block is more critical.

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