

The Short-Lasting Analgesia and Long-Term Antihyperalgesic Effect of Intrathecal Clonidine in Patients Undergoing Colonic Surgery

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In this study, we investigated the antihyperalgesic effect of clonidine after surgery. Sixty patients undergoing right colic resection were studied. Patients were randomized to receive prior to general anesthesia a 2-mL intrathecal (IT) injection of 300 μ g of clonidine or saline, or 10 mg of bupivacaine. General anesthesia was achieved using a target concentration propofol infusion and monitored using bispectral index. Postoperative analgesia was provided by morphine IV given through a patient-controlled analgesia device. Postoperative analgesia was assessed by morphine requirements and visual analog scale pain scores at rest, cough, and movement during the first 72 h. Mechanical hyperalgesia was measured by von Frey filaments. Patients were questioned regarding residual pain at 2 wk, 1, 6, and 12 mo. The patient-controlled analgesia morphine require-

ments were significantly smaller in the IT clonidine group (31.5 ± 12 versus 91 ± 25.5 and 43 ± 15 mg, respectively, in groups clonidine, saline, and bupivacaine: $P < 0.05$ at 72 postoperative hours). The area of hyperalgesia at 72 h was 3 ± 5 cm² in the clonidine group versus 90 ± 30 and 35 ± 20 cm² in the saline and bupivacaine groups ($P < 0.05$). At 6 mo, fewer patients in the clonidine group experienced residual pain than in the saline group (0 of 20 versus 6 of 20, $P < 0.05$). We conclude that both intraoperative spinal clonidine and bupivacaine improve immediate postoperative analgesia. IT clonidine was, however, more potent than IT bupivacaine to reduce postoperative secondary hyperalgesia.

(Anesth Analg 2005;101:566–72)

Tissue injury induces central nervous system changes that can lead to increased pain perception. In patients undergoing elective surgery, strategies aimed to reduce this phenomenon are particularly important because postoperative pain intensity correlates with the development of residual pain, a symptom that markedly affects patients' quality of life (1). Numerous studies have examined techniques or medications that improve immediate postoperative pain relief. This improvement has been assessed using common clinical variables, such as a reduction in pain scores and/or early postoperative analgesic needs. However, few trials have considered specific variables reflecting the degree of central nervous system sensitization, measured as the area of hyperalgesia surrounding the surgical

wound, or even long-term residual pain. In a previous study, using the same design, we were able to confirm the antihyperalgesic of small-dose systemic ketamine (2). In the present study, we investigated whether spinal clonidine exerts an antihyperalgesic effect in the perioperative period. This α_2 -adrenergic agonist is a well recognized analgesic adjuvant that provides a greater analgesic effect with neuraxial as compared with systemic administration (3,4). Moreover, antihyperalgesic properties have been demonstrated in animal models and volunteer studies after spinal administration of the drug (5,6).

Methods

Adult patients, 65–70 yr old, undergoing curative surgical resection of an adenocarcinoma of the right colon (xypho-pubic incision) were considered. Severe hepatic, renal, cardiovascular, psychological disorders, use of cardiovascular drugs that potentially interact with clonidine, such as β -blockers or conversion enzyme inhibitors, chronic pain syndrome, alcoholism, or inability to understand the study protocol were

This work was exclusively supported by the Department of Anesthesiology of the University of Louvain, St. Luc Hospital.

Accepted for publication January 11, 2005.

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DOI: 10.1213/01.ANE.0000157121.71808.04

exclusion criteria. Patients were classified as ASA physical status 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.

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

Each patient was premedicated with lorazepam 1 mg sublingual 12 h before and approximately 1 h before surgery. Before general anesthesia, as determined by a table of random numbers, the patients received one of the following glucose-free isobaric intrathecal (IT) solutions (volume injected = 2 mL): either 300 μ g of clonidine (clonidine group) or saline (saline group) or 10 mg of bupivacaine (bupivacaine group). The IT technique was performed in all the patients placed in the right lateral position. The dura was punctured using a 25-gauge pencil-point needle (Becton-Dickinson, Franklin Lakes, NJ) oriented with the orifice facing cephalad at approximately the L3-4 interspace. The IT injection of the solution was assessed by visualization of a cerebrospinal fluid reflux through the needle. After IT injection, patients were placed in the supine position. All studied solutions were prepared by an anesthesiologist who was not involved in the patient's care. The patient, the anesthesiologist, and the research nurse who evaluated the analgesia were blinded to the study solutions. The anesthesiologist who delivered anesthesia was also blinded but the pharmacological properties of the different drugs tested precluded strict blinding.

All patients received general IV anesthesia with propofol (target control infusion 4 μ g/mL to facilitate tracheal intubation, followed by 2 μ g/mL) and oxygen/air mixture (fraction of inspired oxygen 40%). Tracheal intubation was performed using lidocaine hydrochloride 1 mg/kg 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. In case of inadequate intraoperative analgesia (more than a 20% increase in systolic arterial blood pressure [SBP] or heart rate [HR] occurring concomitantly with surgical noxious stimulation), additional boluses of IV sufentanil (2.5 μ g) were given.

The intraoperative discovery of an extended tumor resulted in the patient's exclusion.

After recovery of awareness, patients were connected to an IV PCA pump set to deliver 1.5 mg of

morphine per demand with 7-min lockout time and maximal allowed dose of 30 mg per 4 h.

Early postoperative analgesia was assessed using the following variables:

The cumulative number of met and unmet PCA morphine demands at 12, 24, 36, 48, and 72 h.

The pain VAS scores at rest, at cough, at mobilization assessed by a blinded observer at 2, 6, 12, 24, 48, and 72 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. (7). 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 at which 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 5-cm distance around the abdominal incision. The observations were translated on graph paper and the surface area was calculated.

The incidence and intensity of postoperative residual pain was evaluated at 2 wk, 1 mo, 6 mo, and 1 yr 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 every day? and which one? Do you take analgesic medications occasionally (at least 3 times per week)? and which one?

If no: Do you feel particular sensations from the scar area? Itching, burning, sensibility at rest or after mobilization.

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 with the help of a research nurse. Each time, both modes were used.

Perioperative complications, including postoperative oversedation and adverse cardio-circulatory events, were recorded. Moderate hypotension during anesthesia was defined as a 20% reduction of the baseline SBP (as measured the day before surgery with the patient lying quiet for at least 15 min); major hypotension, defined as a 30% reduction of the baseline SBP; moderate bradycardia, defined as a HR decreasing between 50 and 40 bpm; and severe bradycardia, defined as HR decreasing to <40 bpm. These adverse hemodynamic events were treated using fluid

Table 1. Demographic Data

	Clonidine (n = 20)	Saline (n = 20)	Bupivacaine (n = 20)
Age (yr)	66 ± 5	65 ± 4	65 ± 5
Weight (kg)	69 ± 11	71 ± 5	72 ± 8
Height (cm)	167 ± 10	165 ± 10	167 ± 12
Male/female	10 /10	8 /12	9 /11

Results are means ± SD.

supplementation, ephedrine IV bolus 0.1 mg/kg or atropine 0.01 mg/kg when appropriate.

Sedation was evaluated using a 3-point scale (score 1 = spontaneously awake, score 2 = asleep but easily arousable by verbal command, score 3 = asleep and not easily arousable by verbal command).

Statistical analysis was performed with Statistica for Windows (version 5; Statsoft, Tulsa, OK). Statistical power calculations ($\alpha = 5\%$, $\beta = 10\%$) based on our previous studies using this methodology (2) suggested that a group size of 20 should detect a difference of at least 15 cm² in the surface of hyperalgesia. Parametric data (demographic data, time elapsed before first analgesic requirement, cumulative analgesic demands, morphine consumption, surface of hyperalgesia) were analyzed using analysis of variance (ANOVA) and ANOVA for repeated measures. Gender difference was tested using multivariate ANOVA. The normal distribution of the data was assessed according to the Kolmogorov-Smirnov test. *Post hoc* comparisons were made using the Tukey honestly significant difference test. Nonparametric data (VAS, satisfaction scores) were conducted with Kruskal-Wallis one-way ANOVA on ranks. Comparisons of the observed proportions were performed using χ^2 analysis and the Fisher's exact test with Yates correction if appropriate. Results are expressed as mean ± SD or as otherwise specified. A *P* value < 0.05 was considered to be statistically significant.

Results

The study protocol was proposed to 68 consecutive patients. One refused to participate and seven were excluded because of inability to understand the study protocol. All involved patients completed the postoperative pain survey. The demographic data are summarized in Table 1. Patients in the clonidine and bupivacaine groups required significantly less hypnotic supplementation than those in the saline group (number of propofol supplementations 0.8 ± 1 and 2.6 ± 1.3 versus 6.5 ± 1.6 , $P \leq 0.05$). The same observation was made when considering the intraoperative analgesic request (0.1 ± 0.3 and 1.2 ± 1.0 versus 5.0 ± 1.4 in groups clonidine, bupivacaine, and saline, respectively; $P \leq 0.05$). Surgical procedures were uneventful,

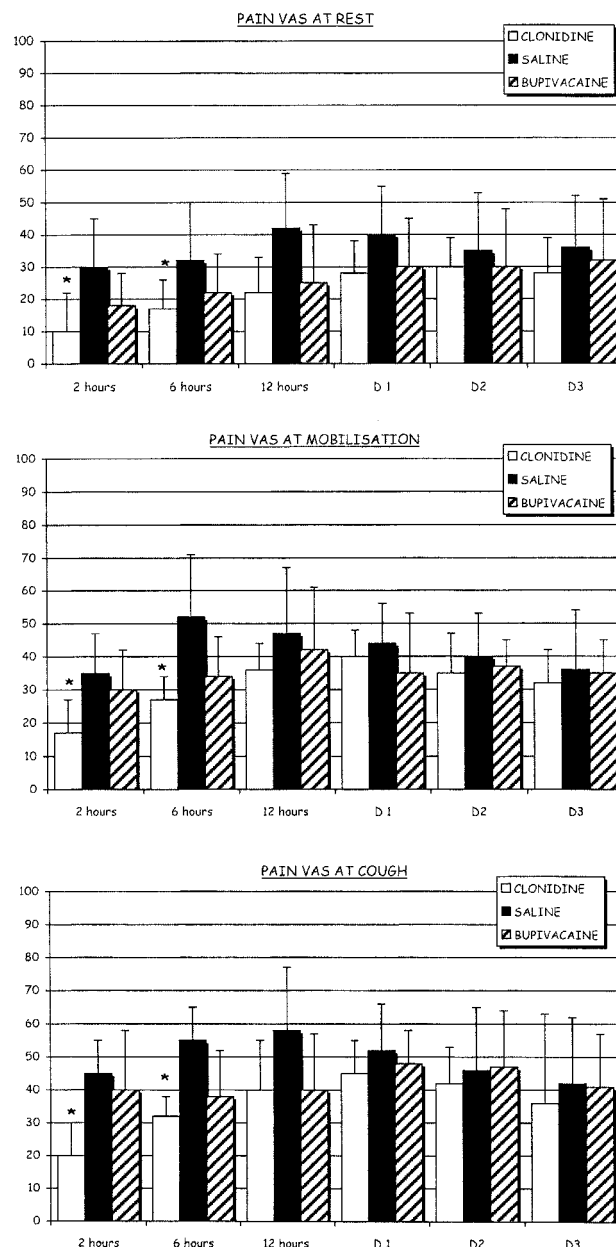


Figure 1. Pain visual analog scale (VAS) scores at rest, mobilization, and cough. Pain VAS scores were significantly lower in the clonidine group during the first 6 postoperative hours than those in the saline group (* $P \leq 0.05$ clonidine versus saline group).

particularly in that no patient required packed red blood cells transfusion.

Time to first analgesic request was significantly longer in the clonidine group when compared with the bupivacaine and the saline group (119 ± 65 versus 72 ± 53 and 44 ± 29 min, $P \leq 0.05$). Pain VAS scores at rest, at cough, and at mobilization were significantly lower in the clonidine group during the first 6 postoperative hours than those in the saline group ($P \leq 0.05$) (Fig. 1). PCA opioid requests (Fig. 2) were significantly fewer in patients of the

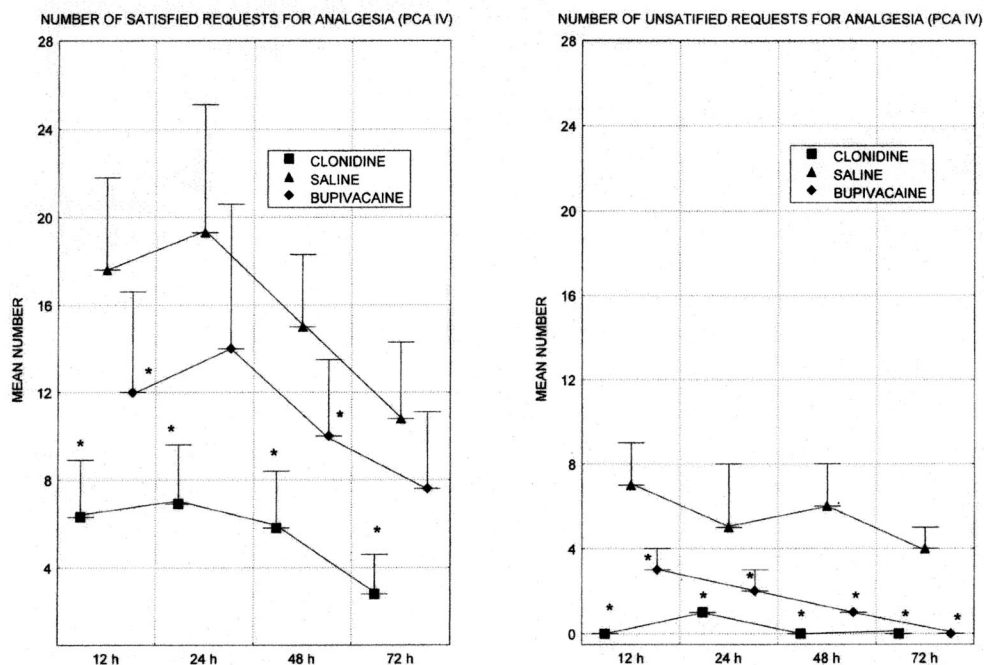


Figure 2. Number of met and unmet patient-controlled analgesic (PCA) opioid requirements at different time periods. The number of PCA opioid requests was significantly larger in the saline group (* $P < 0.05$ from saline group).

clonidine group compared with the saline control ($P \leq 0.05$). A similar but less pronounced effect was observed in patients treated with bupivacaine ($P \leq 0.05$). Consequently, the PCA morphine requirements were significantly less in the IT clonidine group (31.5 ± 12 versus 91 ± 25.5 and 43 ± 15 mg, respectively, in groups clonidine, saline, and bupivacaine: $P < 0.05$ at 72 postoperative hours). At any time considered, the area of hyperalgesia was significantly larger in saline patients when compared with both other groups. A significant difference was also recorded between the clonidine group and the bupivacaine group at 48 and 72 h ($P < 0.05$) (Table 2).

Significantly fewer patients had residual pain at the surgical site at 2 wk, 1 mo, and 6 mo after clonidine treatment than patients in the saline group ($P < 0.05$) (Fig. 3). Patients in the bupivacaine group experienced less residual pain at 2 wk and 1 mo than patients in the saline group ($P < 0.05$) (Fig. 3). In all patients complaining of residual pain, paracetamol or occasionally paracetamol plus codeine (four patients) was sufficient to alleviate pain. Six patients reported low back pain during the observation period (two patients per group). Five of these patients reported an exacerbation of preoperative low back pain. Occasional medications or physiotherapy were required to relieve this symptom. When considering patients' problems other than pain, the most frequent ($\pm 25\%$ of patients per group) complaints were related to the surgical procedure itself (i.e., transit disturbances, or diarrhea). This was independent of the study groups.

The incidence of intraoperative adverse hemodynamic events was significantly more frequent in the IT

Table 2. Area of Hyperalgesia (cm^2) after 24, 48, and 72 h

	Clonidine (n = 20)	Saline (n = 20)	Bupivacaine (n = 20)
24 h	$0.7 \pm 2.4^*$	21.2 ± 16.5	$3.0 \pm 5.2^*$
48 h	$1.6 \pm 3.9^{*+}$	55.2 ± 20.4	$19.2 \pm 14.3^*$
72 h	$2.2 \pm 4.9^{*+}$	90.0 ± 27.5	$31.7 \pm 19.0^*$

Results are means $\pm$ SD.

* $P < 0.05$: groups clonidine and bupivacaine versus saline.

† $P < 0.05$: group clonidine versus bupivacaine.

clonidine group. Seven episodes of moderate hypotension were recorded in the clonidine group versus 2 and 3 in the saline and bupivacaine groups ($P < 0.05$). Only 2 episodes of major hypotension were noted (1 in group clonidine and 1 in group saline) ($P =$ not significant). Administration of ephedrine and/or fluid supplementation corrected all the hypotensive episodes. Moderate bradycardia without hypotension was frequently observed in clonidine-treated patients. No postoperative adverse events were recorded. When considering the sedation scale, none of the patients considered reached a score of 3 at any study time.

During the 1-yr postoperative observation period, none of the recruited patients died. One patient (bupivacaine group) presented with transient cerebral ischemia after 8 mo. Another (clonidine group) experienced myocardial ischemia without infarction at 6 mo.

Outcome variables such as area of hyperalgesia and morphine PCA consumption were tested for gender differences but no significant difference was apparent.

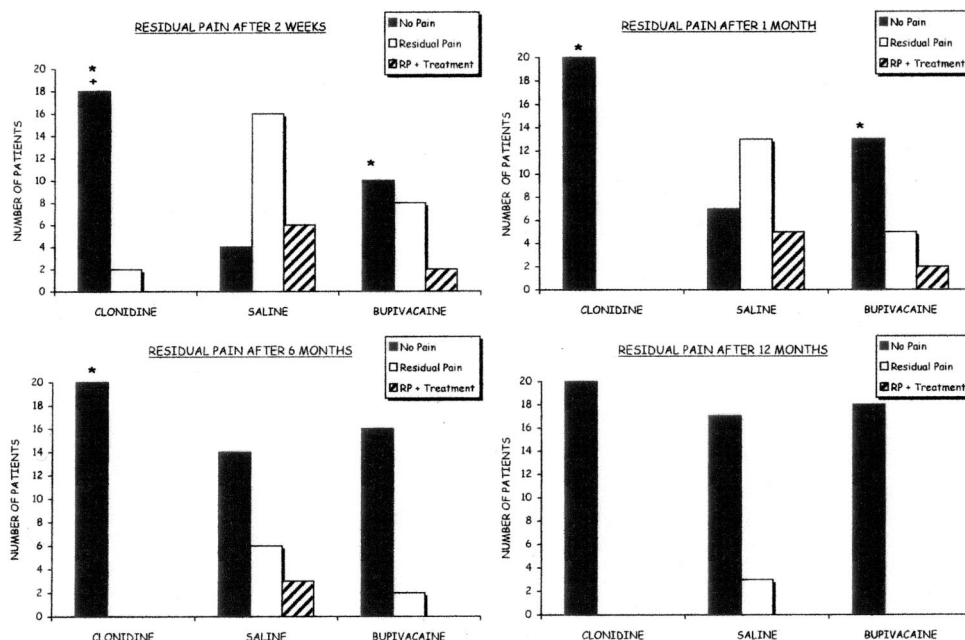


Figure 3. Postoperative residual pain (RP) (requiring treatment or not) at 2 wk, 1, 6, and 12 mo (* $P < 0.05$ from saline group, + $P < 0.05$ clonidine versus bupivacaine group).

Discussion

The results of this study were that spinal clonidine, in addition to a transitory analgesic effect, possesses antihyperalgesic properties resulting in a reduction of area of secondary hyperalgesia around the wound and a reduction of residual pain for up to six months in the postoperative period.

For many years, the α_2 -adrenergic agonist clonidine has been considered as an efficient analgesic adjuvant for perioperative pain management and particularly loco-regional techniques (3). The mechanisms underlying this antinociceptive effect rely on the modulation of pain perception, principally at the spinal level (4). Exogenous clonidine mimics the effect of endogenous norepinephrine and activates descending inhibitory pathways. Several experimental and clinical studies have shown the importance of post-attributional secondary hyperalgesia as an objective measure of central sensitization in pain perception. Central nervous system sensitization has been incriminated in the development of postoperative residual pain, as was the involvement of postoperative pain itself (1). Our results support a potent effect of IT clonidine to blunt the development of secondary wound hyperalgesia in patients undergoing colic surgery. This is in accordance with experimental work using α_2 -adrenergic agonists performed both in a validated model of incisional pain (5) and also in volunteers in whom IT but not IV clonidine reduced capsaicin hyperalgesia (6). The mechanism underlying this specific antihyperalgesic effect might result from an interaction with the "hyperalgesic neurons" of the marginal layer (lamina I) of the spinal dorsal horns. These neurons have been recently reported to be under the control of both

AMPA (excitatory) and γ -aminobutyric acid (GABA) (inhibitory) receptors (8). Endogenous norepinephrine, and its derivatives such as exogenous clonidine promote the GABAergic inhibitory system at both central and spinal sites (9–11). Hence, perimedullar administration of clonidine has probably contributed to silencing these hyperalgesic neurons activated by surgery.

Perimedullar administration of a drug can be achieved by using the epidural or the IT route. We chose the IT route for the following reasons: the antinociceptive potency of clonidine is higher compared with epidural administration. In volunteers, using capsaicin-induced hyperalgesia and allodynia as a model of central sensitization and noxious thermal stimulus as a model of acute pain, Eisenach et al. (12) demonstrated that there is a more than six-fold potency ratio of IT/epidural administration of clonidine concerning acute pain modulation, and a less than twofold potency ratio for mechanical hypersensitivity. Moreover, our previous experience with epidural clonidine as the sole analgesic drug supported this assumption (13,14). In these studies, very large doses of epidural clonidine (10 $\mu\text{g}/\text{kg}$ in bolus followed by 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) were required for a comparable surgical procedure to achieve satisfactory perioperative analgesia. In the present study, only 300 μg of IT clonidine was given before anesthetic induction. This was the largest dose administered in a volunteer study (6). In women undergoing cesarean delivery under general anesthesia induced by thiopental and maintained with halothane without any analgesic, Filos et al. (15) evaluated several doses of IT clonidine (up to 450

μg) given for postoperative analgesia. With the 300- μg dose, these authors recorded efficient analgesia (pain VAS scores and time elapsed before rescue medication) lasting 570 ± 76 versus 181 ± 169 minutes in the saline group. In our study, the first analgesic requirement occurred earlier but two facts have to be considered: First, IT clonidine was given before induction of anesthesia (consequently, the duration of anesthesia has to be added to the postoperative time). Second, laparotomy for colic surgery results in a much more painful stimulus than low transverse Pfannenstiel incision for cesarean delivery. Nevertheless, in patients experiencing postoperative abdominal pain, a single dose of spinal clonidine can provide significant immediate postoperative analgesia. Moreover, early analgesic properties of spinal clonidine have also contributed to its long-lasting antihyperalgesic effect. IT administration of analgesic drugs before surgery prevents nociceptive input from the injured site reaching the spinal cord and triggering hypersensitivity (16). The net result is a reduced central sensitization and hence an improved global postoperative pain experience (pain VAS scores, morphine PCA requirements, area of hyperalgesia) along with a reduced incidence of postoperative residual pain. This observation confirms the correlation by Perkins and Kehlet (1) in their meta-analysis between the intensity of acute postoperative pain and possible chronic evolution of pain symptoms. The decreased antihyperalgesic efficacy of bupivacaine when compared with IT clonidine is not surprising. IT bupivacaine produces more complete neuronal blockade than IT clonidine (17). Meanwhile, in contrast to IV lidocaine, spinal local anesthetics lack antihyperalgesic effects (18,19). Nevertheless, IT bupivacaine is undoubtedly more efficient than IV anesthesia for immediate postoperative analgesia.

Another explanation for the reduced hyperalgesia recorded in both IT groups is the important reduction of the amount of perioperative opioids allowed by this technique in comparison with the saline group. According to the recent theory on opiate-induced hyperalgesia, this may be of some importance (20).

In our study, the IT administration of 300 μg of clonidine was not associated with serious side effects. Particularly, no postoperative oversedation was recorded. The only noticeable problem was the increased incidence of intraoperative moderate hypotensive events. This has been previously noted by Eisenach et al. (6,12) in a volunteer study using the same dose of IT clonidine. Clonidine interferes with the control of arterial blood pressure at peripheral, spinal, and central sites (3). Nevertheless, in our study, all the patients received propofol during anesthesia at the same target concentration infusion

and patients in the clonidine group required almost no supplemental anesthetics based on bispectral index criteria; this increased incidence of adverse cardio-circulatory events may be, at least partially, ascribed to a deeper level of anesthesia. The observation that none of the patients in the clonidine group developed postoperative hypotension is in accordance with this explanation.

In conclusion, our results clearly demonstrate that both intraoperative spinal clonidine and bupivacaine improve immediate postoperative analgesia. IT clonidine was, however, more potent than IT bupivacaine for reducing postoperative secondary hyperalgesia in patients recovering from abdominal surgery.

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