

The use of intraoperative epidural or spinal analgesia modulates postoperative hyperalgesia and reduces residual pain after major abdominal surgery

P. LAVAND'HOMME and M. DE KOCK

Abstract : *Introduction :* The use of intraoperative multimodal analgesia has clearly improved postoperative pain control, mortality and morbidity after major surgical procedures. However, very few clinical trials have studied the longterm impact of intraoperative epidural or spinal analgesia on chronic postsurgical pain (CPSP) development. Even less studies have evaluated the modulatory effect of intraoperative neuraxial analgesia on objective changes (i.e. mechanical hyperalgesia) reflecting central sensitization.

Methods : The present work compares general anesthesia alone (GA group) versus general anesthesia combined to either intraoperative epidural analgesia (EPID group : combination of bupivacaine, sufentanil and clonidine 1µg/kg) or spinal analgesia (IT group : either bupivacaine or clonidine 300 µg) on the development of secondary mechanical hyperalgesia and the incidence of CPSP after major abdominal surgery. Data analyzed in the present work involve adult patients undergoing surgical resection of rectal adenocarcinoma who participated in three previously published randomized trials.

Results : Intraoperative epidural and particularly spinal analgesia reduced both incidence ($p < 0.05$ between GA alone and spinal analgesia) and extent (area) of secondary mechanical hyperalgesia surrounding the wound at 48h and 72 h after surgery. The use of intraoperative epidural and spinal analgesia also reduced CPSP incidence. Postoperative area of mechanical hyperalgesia seems positively correlated with the incidence CPSP.

Conclusion : An effective intraoperative neuraxial block of nociceptive inputs from the wound using multimodal analgesia - specifically when involving spinal analgesics and antihyperalgesic drugs - contributes to prevent central sensitization and hence reduces CPSP after major abdominal procedures.

Key words : Epidural analgesia ; spinal analgesia ; chronic postsurgical pain ; secondary hyperalgesia.

INTRODUCTION

To date, the efforts in anesthesiology practice have been directed toward an increase of patients' safety and a reduction of adverse events occurring

in the immediate perioperative period. The use of multimodal analgesia, which describes any combination of two or more analgesic modalities, has clearly improved postoperative pain control and reduced analgesia-related adverse effects (1). For major surgical procedures, epidural or intrathecal analgesia combined with general anesthesia significantly improves postoperative mortality (overall mortality reduced by about one third) and morbidity (reduction of the incidence of deep vein thrombosis, pulmonary embolism, pneumonia...) (2). Among the adverse outcomes associated to surgery, persistent pain has received little attention until recently. However, surgery is the origin of chronic pain in 25% of the patients attending the Pain Clinics (3) and the estimated incidence of chronic postsurgical pain (CPSP) lays between 11 and 47% according to the different surgical procedures (4, 5). Among the risk factors to develop CPSP, the severity of acute postoperative pain seems the most striking one (4, 5). Still, despite the obviously simple nature of surgical incision, perioperative and more specifically postoperative pain today remains undervalued and poorly treated (6). Pain caused by incision presents with unique features and differs from inflammatory and neuropathic pain (7). Among these features, hyperalgesia which is the clinical expression of sensory system sensitization, is clearly part of the pain perceived by the patients

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after surgery and clinically important for two reasons (8). First, hyperalgesia increases the amount of postoperative pain because of enhancement of given noxious inputs, resulting in higher morbidity, stress and suffering. Second, increased central nervous system excitability is susceptible to induce permanent modifications in the system leading to the development of persistent pain (9). Specifically, secondary hyperalgesia, an exaggerated response observed only to mechanical stimuli applied in uninjured tissues surrounding the incision, is considered a consequence of central sensitization. Secondary hyperalgesia results from enhanced response of spinal dorsal horn neurons to peripheral inputs, with magnitude and duration related to the degree of tissue injury (10-12). Consequently, secondary hyperalgesia may predict a risk for patients to develop persistent pain after surgery. To date, very few clinical trials have studied the longterm impact of intraoperative epidural or spinal analgesia, specifically on CPSP development (postoperative pain lasting more than 3 months after the procedure). Even less studies have use *Quantitative Sensory Testing* (by example punctuate mechanical stimulation surrounding injured tissues) (13) to quantify nervous system input-response relationship, hence to assess the objective sensory changes associated to surgical injury. In the present work, we have intended to evaluate the benefit of a short-term intraoperative treatment, either epidural or spinal analgesia, on a long-term outcome of patients defined as residual pain (CPSP). Further, by measuring secondary hyperalgesia surrounding the wound, we have tried to detect postincisional spinal sensitization and to question the impact of

intraoperative epidural or spinal analgesia on the modulation of postoperative central neuroplasticity.

MATERIALS AND METHODS

The present work sought to compare the effect of general anesthesia alone (GA group) *versus* general anesthesia combined to either intraoperative epidural analgesia (EPID group) or intraoperative spinal analgesia (IT group) on the development of secondary mechanical hyperalgesia and the incidence of CPSP after major abdominal surgery. Data analyzed in the present study involve adult patients undergoing curative surgical resection of rectal adenocarcinoma (xypho-pubic incision) who participated in three previously published randomized trials (14-16) and for whom similar standardized protocols of anesthesia and surgical procedure allow a comparative analysis. Table 1 describes the different groups of patients - general anesthesia alone (no neuraxial analgesia or GA group), general anesthesia with intraoperative epidural (EPID group) or intrathecal (IT group) analgesia - and mentions the respective origin of the data used. For all the studies, Ethical Committee approval and patient informed consent had been obtained. Severe hepatic, renal, cardiovascular, psychological disorders, pre-existing pain syndrome and/or analgesic treatment, alcoholism or inability to understand the study protocol were exclusion criteria. Patients were classified as American Society of Anesthesiologists physical status I, II or III. Tracheal intubation was performed under propofol, sufentanil 2.5 µg and atracurium and anesthesia

Table 1

Groups of patients and corresponding data from clinical trials (references of the clinical trials are in brackets ())

	GA group	EPID group	IT group
Age (years)	59 ± 6	60 ± 9	65 ± 6
Males/Females (n)	20 / 20	22 / 18	19 / 21
Intraoperative analgesia	No neuraxial analgesia : Group IV-IV (n = 20) (16) Group IT saline (n = 20) (15)	Epidural analgesia : Group EPI-IV (n = 20) (16) Group I (n = 20) (14)	Spinal analgesia : IT bupivacaine (n = 20) (15) IT clonidine (n = 20) (15)
Postoperative analgesia	IV PCA morphine	IV PCA morphine	IV PCA morphine

(14) DE KOCK *et al.*, PAIN, 2001. Group 1 received intraoperative epidural analgesia with bupivacaine 0.5%-sufentanil-clonidine 1 µg/kg combination, no intravenous ketamine.

(15) DE KOCK *et al.*, ANESTH. ANALG., 2005. Groupe IT bupivacaine received 10 mg hyperbaric bupivacaine and group IT clonidine received 300 µg intrathecal clonidine, no intravenous ketamine.

(16) LAVAND'HOMME *et al.*, ANESTHESIOLOGY, 2005. Group IV-IV received no neuraxial analgesia but intraoperative intravenous ketamine-lidocaine infusion at antihyperalgesic dose, group EPI-IV received intraoperative epidural analgesia with bupivacaine 0.5%-sufentanil-clonidine 1 µg/kg and intravenous ketamine at antihyperalgesic dose.

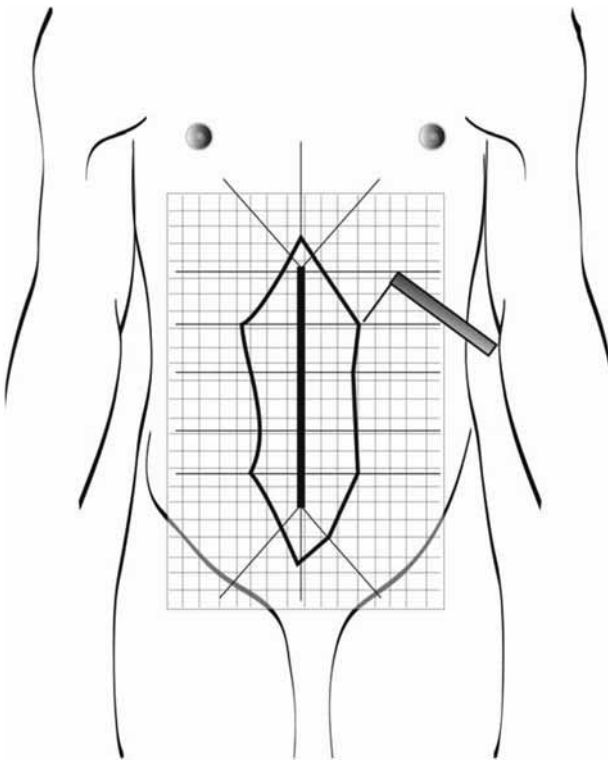


Fig. 1. — Mapping of the area of secondary punctuate mechanical hyperalgesia surrounding the wound (with the use of von Frey filament) after xypho-pubic incision for abdominal colorectal surgery (from LAVAND'HOMME *et al.*, ANESTHESIOLOGY, 2005 (16)).

maintenance was realized with propofol (3 mg/kg/h) and oxygen/air mixture (fiO₂ 40%). During the surgical procedure, additional boluses of propofol (0.5 mg/kg) or sufentanil were allowed to maintain a bispectral index between 55 and 65. After surgery completion, in all the patients, postoperative analgesia was provided by Patient-controlled analgesia (PCA) with intravenous morphine.

Evaluation of postoperative secondary hyperalgesia

The area of hyperalgesia for punctuate mechanical stimuli around the incision was measured at 24, 48, 72 hours according to the method described by Stubhaug (17). 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 appeared was marked and the distance to the incision was measured. If no change in sensation appeared, 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. All the observations were translated on graph paper to calculate the surface area.

Evaluation of residual pain

The incidence and importance of postoperative residual pain located at the scar area was evaluated at one and 6 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? everyday 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... This enquiry was performed by the research nurse with phone call and confirmed by mail.

STATISTICAL ANALYSIS

Comparison of the observed proportions were performed using Chi-squared analysis with corrections for multiple groups. Correlation was performed with linear regression and Spearman test. A probability (*P*) value of less than 0.05 was considered to be statistically significant.

RESULTS

The different groups were matched for age, sex ratio and number of patients (Table 1). The evaluation of postoperative mechanical hyperalgesia demonstrated that the incidence of secondary punctuate hyperalgesia surrounding the wound was significantly reduced at 48h and 72h postsurgery in patients who received intraoperative spinal analgesia with bupivacaine or clonidine ($p < 0.05$ with general anesthesia alone, Fig. 2a). Although epidural analgesia also contributed to decrease the incidence of secondary hyperalgesia, it was no statistically significant (Fig. 2a). At both one month and 6 months after surgery, the percentage of patients with residual pain was significantly decreased in the groups who received either intraoperative epidural analgesia or spinal analgesia (Fig. 2b). The incidence of CPSP, at 6 months after colorectal resection was 38.5% in GA group, 13.5% in EPID group and 11% in IT group. At 12 months after surgery, CPSP was present in 23% of patients who underwent surgery without intraoperative neuraxial block and 1% or less in patients who benefited from

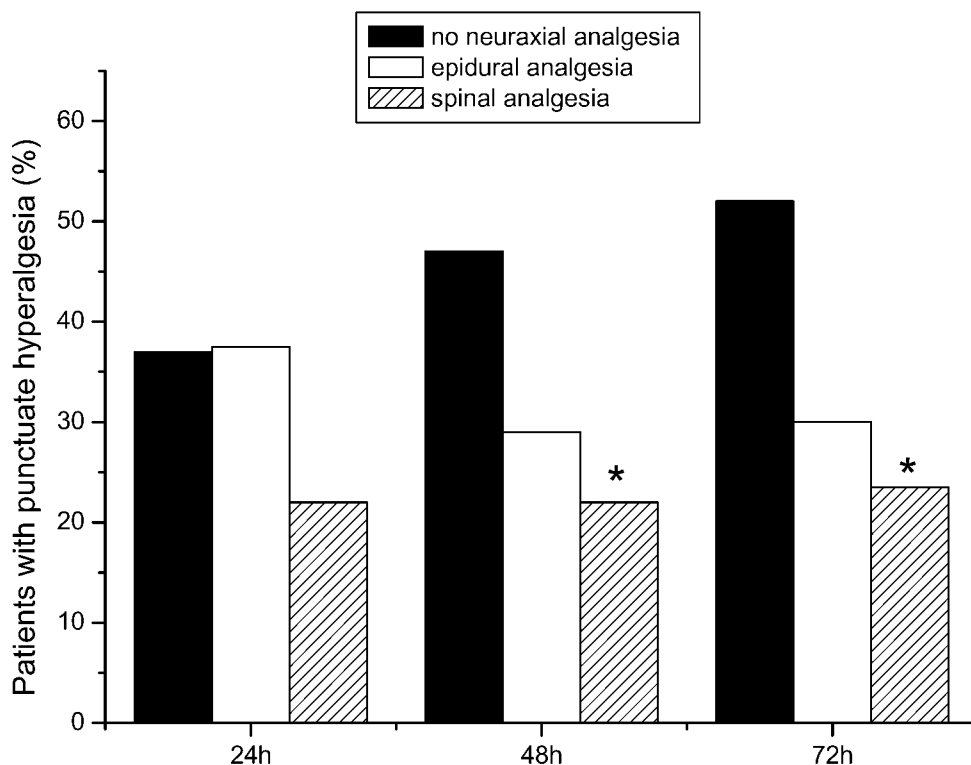


Fig. 2a. — Percentage of patients presenting with postoperative punctuate mechanical hyperalgesia in relation to the different intraoperative treatments. All the patients received general anesthesia combined to : no neuraxial analgesia (GA group), epidural analgesia (EPID group) or spinal analgesia (IT group). $P < 0.05$ with the group without neuraxial analgesia at the same postoperative time.

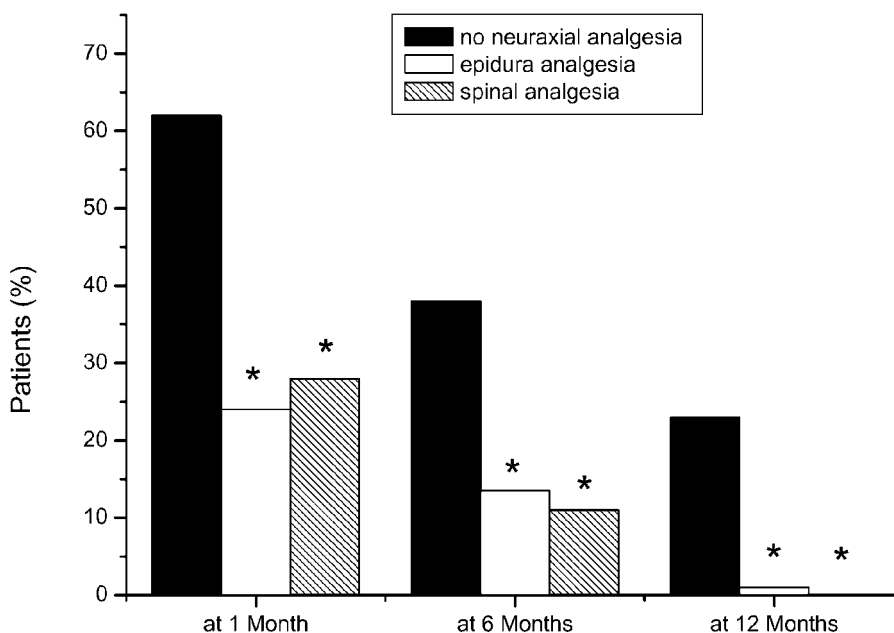


Fig. 2b. — Percentage of patients presenting with residual pain at 1, 6 and 12 months in relation to the different intraoperative treatments. All the patients received general anesthesia combined to : no neuraxial analgesia (GA group), epidural analgesia (EPID group) or spinal analgesia (IT group). $P < 0.05$ with the group without neuraxial analgesia at the same postoperative time.

intraoperative neuraxial analgesia, either epidural or intrathecal analgesia ($p < 0.05$ with GA group). Patients who received general anesthesia alone also displayed larger area of secondary hyperalgesia

while intraoperative epidural and specially intrathecal analgesia reduced the area of mechanical hyperalgesia ($p < 0.05$ between EPID group – IT group and GA group) (Fig. 3). The extent of the area of

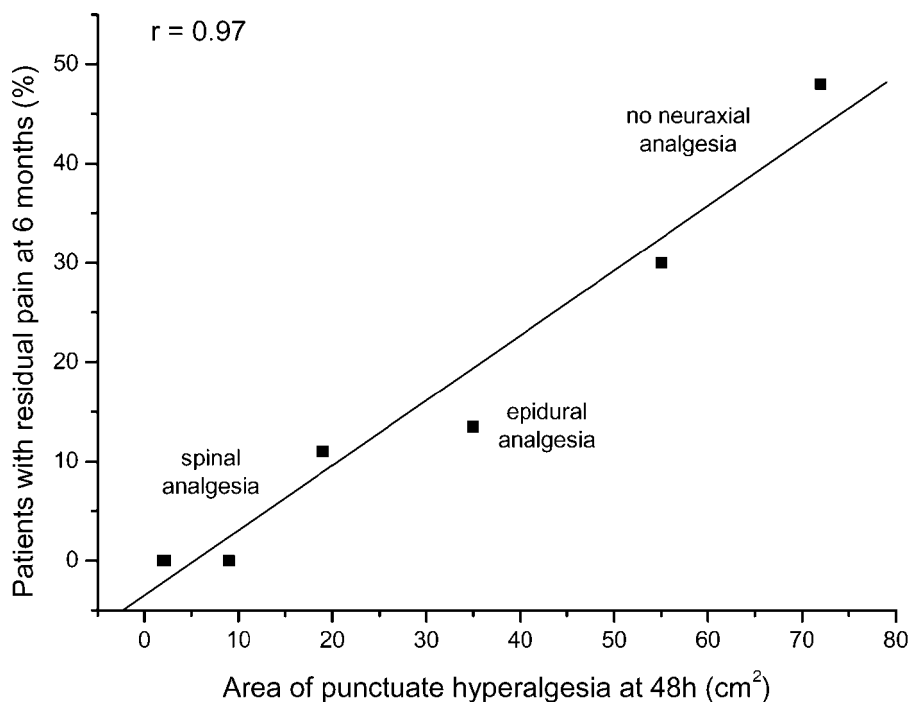


Fig. 3. — Relationship between the area of punctuate hyperalgesia surrounding the wound and the percentage of patients presenting with chronic postsurgical pain at 6 months after surgery in the different intraoperative treatment groups. All the patients received general anesthesia combined to : no neuraxial analgesia (GA group), epidural analgesia (EPID group) or spinal analgesia (IT group). $P < 0.05$ between epidural-spinal analgesia and the group without neuraxial analgesia.

punctuate hyperalgesia surrounding the wound was significantly correlated with the likelihood for the patients to experience CPSP at six months after the surgery (Fig. 3).

DISCUSSION

The present analysis of data clearly shows that multimodal analgesia, particularly the use of intraoperative epidural or intrathecal analgesia combined with general anesthesia, reduces the development of central sensitization after major surgical procedure. This reduction of central sensitization is clinically expressed as an objective decrease of both the incidence and the extent of mechanical secondary hyperalgesia surrounding the wound and correlates with a reduction of the incidence of residual pain. The risk of chronic pain after gastrointestinal surgery situates between 11% (18) and 18% (95% CI : 13-23%) (19) at four to five years after surgery. Our results showing an incidence of 23% after one year are in agreement. Interestingly, while the aforementioned published papers do not mention the anesthetic and analgesic techniques used, we have found that an intraoperative combination of

neuraxial analgesia, either epidural or intrathecal block, with general anesthesia allows to significantly reduce the risk for CPSP. Very few reports mention the effect of spinal analgesia on residual pain after surgery. After cesarean section, however, patients with pain at 10 months had more often undergone the procedure under general anesthesia alone (37% presenting with CPSP *versus* 17% in the group under spinal anesthesia) (20). Several reports have assessed the impact of intraoperative epidural analgesia on CPSP with divergent results. Thoracic surgery which is associated to one of the highest risk for CPSP, between 30 to 40% (4), has been extensively studied with the use of thoracic epidural analgesia (TEA). Intraoperative TEA significantly reduced CPSP in the studies from Obata (21) and Tiippana (22) while TEA did not provide any benefit in other trials (23). After radical prostatectomy, intraoperative epidural analgesia improved longterm outcome (24). In contrast, epidural analgesia was not associated to reduced pain and disability at six months after major gynecologic surgery (25). The disparity between these results might be related to the different drugs and doses which have been used to block noxious input to the central nervous system. Numerous studies have used TEA

with opioid alone or low concentration of local anesthetic to minimize the risk of sympathetic block and secondary hypotension in fragile patients undergoing thoracotomy or cardiac surgery. In a clinical trial considering intraoperative epidural analgesia for digestive surgery, Aida and colleagues have shown that morphine alone was not very effective (26). Secondary hyperalgesia, the clinical expression of central nervous system sensitization, is mediated by peripheral nerve fibers but when it has fully developed, becomes independent of peripheral neural activity originating from the wound (27). Therefore, early and effective block of noxious inputs from the surgical area seems mandatory to reduce secondary hyperalgesia development. Noxious inputs associated with both thoracic surgery (23) and abdominal surgery (26) are conveyed by segmental (i.e. spinal nerves) and heterosegmental (i.e. vagus and phrenic nerves) innervation. An effective block of these components requires the association of both analgesic and antihyperalgesic drugs. Subanesthetic doses of ketamine strongly potentiate epidural analgesia for digestive surgery (14, 26), either by a supra-spinal effect blocking brain stem sensitization or by an anti-inflammatory effect. Similarly, the addition of clonidine, an α_2 -adrenoceptor agonist which mimics noradrenergic descending inhibitory system (28), to epidural analgesia modulates perioperative cytokine response and inflammatory reaction after colorectal surgery (29). In our study, all the patients with epidural analgesia received a mixture of bupivacaine 0.5% with sufentanil and clonidine. Clonidine possess antihyperalgesic properties, specifically after neuraxial administration. Spinal clonidine reduces hyperalgesia in animal models of incisional pain (30) and intrathecal, but not intravenous clonidine, reduces the area of secondary hyperalgesia after capsaicin injection in human volunteers (31). Considering the reduction of mechanical hypersensitivity, epidural route is almost as effective as spinal route for the administration of clonidine and the dose should be superior to 75 μg (32). Our patients received either intrathecal clonidine 300 μg or epidural clonidine 1 $\mu\text{g}/\text{kg}$. Furthermore, spinal clonidine has been reported as particularly effective to alleviate pain from visceral origin (33). The exact role of secondary hyperalgesia for postoperative pain is not fully understood but as an objective measure of central sensitization, it may predict the risk for persistent pain (34, 35). The present data are in agreement because we have found a positive correlation between the area of mechanical hyperalgesia and the risk for CPSP and also because the

treatments which decrease the incidence of secondary hyperalgesia in patients are associated to less CPSP development. Mechanical hyperalgesia certainly contributes to postoperative pain (9) and severe undermanaged postoperative pain enhances the likelihood for CPSP (5). However, it is worth to note that, treatments which modulate the development of hyperalgesia may not have an impact on postoperative pain measured with the use of visual analog scales (14, 15). In conclusion, the presence and the extension of secondary hyperalgesia may be indicative to the risk of developing CPSP. An effective intraoperative block of nociceptive inputs, either epidural or intrathecal analgesia involving analgesics and antihyperalgesic drugs, contributes to reduce central sensitization, clinically expressed as mechanical hyperalgesia, and the risk for residual pain after major abdominal surgery.

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