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Continuous Local Anesthetic Wound Infusion to Improve Postoperative Outcome

Back to the Periphery?

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EFFECTIVE postoperative analgesia is a prerequisite to enhance the recovery process and reduce morbidity. The use of local anesthetic techniques is well documented to be effective, but single-dose techniques (infiltration, peripheral blocks, neuraxial blocks) have been of limited value in major operations because of their short duration of analgesia. Continuous administration of local anesthetics at various segments in the nociceptive pathway has therefore been introduced and where the relatively demanding continuous peripheral nerve blocks and epidural techniques have proven effective, although with a small risk of complications and relatively high costs. From a theoretical point of view, administration of local anesthetics at the wound site is the most rational approach to reduce the afferent nociceptive barrage and thereby pain and stress responses with their secondary risks of organ dysfunction and morbidity. Therefore, an improved understanding of the analgesic efficacy of continuous wound infusion of local anesthetics and its consequences on outcome is important as reported by Beaussier *et al.*[1] In their double-blind randomized setup, patients undergoing colonic surgery received continuous ropivacaine at 0.2%/10 ml/h for 48 h or saline through a multiholed wound catheter placed in the preperitoneal space. The study has important clinical implications because they assessed in detail relevant outcomes such as patient-controlled analgesia–quantified opioid sparing, level of dynamic analgesia, sleep quality, and recovery of gastrointestinal function, all of which were significantly improved, and duration of hospitalization was reduced (115 *vs.* 147 h) as well. No wound morbidity or ropivacaine toxicity was observed.

Hitherto, no analgesic technique has fulfilled all requirements of optimal efficacy—no side effects, low costs, high patient compliance, and improvement in outcome—and consequently, multimodal analgesic techniques have been introduced with a focus on opioid sparing to improve analgesia and recovery.[2] As documented by Beaussier *et al.*[1] as well as in randomized studies with different continuous local anesthetic wound infusion techniques,[3] the available data have almost consistently shown improved analgesia across a range of procedures and with a very low (approximately 1%) technical failure rate and zero reported toxicity. Most importantly, wound infection rates have not increased,[3] and patient compliance is acceptable. Unfortunately, the studies previously reported in the literature[3] have not allowed sufficient analyses on postoperative recovery of different organ functions (pulmonary, ileus, mobilization, *etc.*), or a potential reduction in morbidity as well as duration of hospitalization will require further studies because of a lack of well-defined discharge criteria and standardized care and rehabilitation programs according to the concept of fast-track surgery.[4] The report by Beaussier *et al.*[1] therefore represents an important example of how to optimize design for an improved assessment of local anesthetic wound infusion to enhance the postoperative recovery process.

The important question is whether we have enough evidence to more widely recommend continuous local anesthetic wound infusion techniques in our perioperative care programs. The primary risk from peripheral infusions of local anesthetics is direct tissue toxicity such as myotoxicity. Although there are supportive laboratory data, the clinical experience is that such injuries are rare.[5] So far, the benefits clearly outweigh the risks, and the only drawback of the technique is catheter equipment costs, which amount to approximately US $250 per patient. However, this may be acceptable in certain major procedures such as abdominal surgery, provided that the significant improvements in outcome as demonstrated by Beaussier *et al.*[1] can be confirmed by others. The cost of this technique may be further offset by its

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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simplicity. Because the equipment is basic and risk of serious complications is minimal, it is likely that these patients can be treated on the floor without involvement and subsequent cost of an acute pain service. This would not only save charges to the patient, but also allow the acute pain service to focus on patients with more complicated pain management techniques. On the other hand, continuous local anesthetic wound infusion in minor procedures such as inguinal herniorrhaphy may not be cost effective despite proven efficacy.[3] Instead, in such minor procedures we should strive to implement effective oral multimodal nonopioid analgesia,[2] which is more simple to manage and can be continued for a longer period where necessary than the usual wound infusion regimens with 2–3 days' duration.[1,3]

However, as is so often the case, introduction of new analgesic techniques also raises several important questions: What is the optimal concentration and volume of the local anesthetic? (no conclusive procedure-specific dose response studies available); what is the optimal site of placement of the wound catheter? Beaussier *et al.*[1] used preperitoneal placement, which may be rational, and probably the placement should be close to the muscle-facial layer and not in the subcutaneous layer, as demonstrated in one of the few comparative studies.[6] Furthermore, we should not be overoptimistic that these newer techniques alone will provide sufficient dynamic analgesia, and therefore the opioid-sparing effects should be assessed in more detail in different procedures (postoperative nausea and vomiting, sedation, sleep disturbances, *etc.*[1,2]) and combined with other nonopioid analgesics. In addition to these patient-reported outcomes, it will be interesting to examine impact on patient safety from opioid sparing. The Anesthesia Patient Safety Foundation has recently released a position statement highlighting potential risks of respiratory depression with systemic and central neuraxial opioid analgesia.* Use of continuous local anesthetic wound infusion techniques, especially with concomitant use of several nonopioid analgesics,[2] may thus directly improve patient safety. Importantly, the optimal duration of wound local anesthetic infusion must be evaluated together with the effect on relevant outcomes. So far, the literature on the effect of different types of perioperative analgesia on outcome is controversial,[7] most probably because the analgesic techniques have not been sufficiently incorporated into multimodal rehabilitation programs to take advantage of the provided analgesia.[4] Finally, there is a need for comparative studies with other local anesthetic techniques such as epidural analgesia,[7,8] predominantly to assess potential differences in technical failures, costs, and side effects. Comparison with continuous paravertebral blocks and epidural analgesia in thoracic procedures is a good example,[3,9] as well as comparison with peripheral nerve blocks in major orthopedic procedures.[10,11] Therefore, recent data from high-volume incisional multimodal local anesthetic infiltration/infusion[12] is of major interest because of its simplicity, efficacy, and safety, but additional studies are required to assess the relative role of incisional *versus* intraarticular administration in major joint replacement.[12] Other areas of interest could be comparison with systemic administration of local anesthetics.[13]

So far, the promising data on continuous wound infusion of local anesthetics call for a balanced assessment of practicality *versus* other benefits *versus* side effects with other analgesic techniques and agents. This balanced approach to evaluation may become especially valuable because multiple new peripheral analgesics are being developed for postoperative analgesia. Sustained duration local anesthetics may provide up to 96 h of analgesia after a single injection and would further improve on simplicity by removing the requirement for any infusion pump equipment.[14] Additional peripheral pharmacologic agents are also being examined, such as a TRPV1 (capsaicin) agonist for sustained postoperative analgesia after total knee replacement[15] and possible application of peripheral tricyclic antidepressants.[16] All of these represent new, exciting, and potentially valuable means to provide nonopioid analgesia directly to the periphery. However, all must be comprehensively evaluated.

In summary, the peripheral use of continuous wound infusion of local anesthetics represents an effective analgesic technique that, because of its simplicity, may find its way to be an important instrument in our analgesic armamentarium across several major surgical procedures. It is hoped that future research will document in more detail other extra-analgesic benefits on outcomes, such as reduction of postoperative organ dysfunctions and enhanced recovery when integrated into multimodal rehabilitation programs,[4] patient safety, and quality of life and health economics.

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Glucocorticoids for Acute and Persistent Postoperative Neuropathic Pain

What Is the Evidence?

PERSISTENT neuropathic postoperative pain is a major health problem. It is highly important to find therapies that prevent or reduce chronic neuropathic postoperative pain. The current issue of ANESTHESIOLOGY contains an animal study by Li *et al.*[1] that examines the role of a systemic glucocorticoid (triamcinolone acetonide) on aspects of pain and inflammation using the spinal nerve ligation model. This model is traditionally considered a neuropathic pain model, but involves surgery and evokes an inflammatory response linked to pain behavior. In their study, Li *et al.*[1] demonstrate that systemic injections of a glucocorticoid reduce apparent pain behavior, proinflammatory cytokines, overall neuronal firing rate, incidence of bursting activity, and abnormal sympathetic sprouting in dorsal root ganglia.

Proinflammatory cytokines secreted at or near the site of a nerve injury are involved in the development and maintenance of central sensitization and neuropathic pain.[2,3] Glucocorticoids suppress proinflammatory cytokines and induce expression of antiinflammatory cytokines.[1,2,4–6] They also reduce the prostaglandin synthesis by inhibiting phospholipase A_2 and by blocking the expression of cyclooxygenase-2 messenger RNA.[4,6]

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Spinal glial activation stimulates nuclear factor κB, which induces cyclooxygenase-2, release of prostaglandins, and production of proinflammatory cytokines, excitatory amino acids, and growth factors establishing pathologic pain.[5,7,8] By inhibiting glial activation and the activation of nuclear factor κB in animal models, glucocorticoids prevent the development of neuropathic pain behavior.[5,7]

Reduced release of neuropeptides from nerve endings, inhibition of signal transmission in nociceptive C fibers and ectopic discharge from traumatized nerves,[9–11] reduced mechanically induced dysesthesia after nerve injury,[12] improved nerve recovery and regeneration,[12–14] and a dose-dependent rapid inhibitory effect on the voltage-dependent calcium currents in dorsal root ganglion neurons[15] are all documented effects of glucocorticoids that may contribute to analgesia.

Rapid antihyperalgesic effects of glucocorticoids have been demonstrated in animals and humans.[2,16,17] Reduction in neural discharge within seconds to a few minutes due to nongenomic steroid effects on membrane receptors has been observed.[18] These rapid nongenomic effects of glucocorticoids are due, at least in part, to decreased glutamate release and increased release of γ-aminobutyric acid and endocannabinnoids.[19,20] By decreasing glutamate and increasing γ-aminobutyric acid, glucocorticoids would be expected to rapidly cause a marked reduction in excitability of nerve cells.[19] A theoretic possibility is that both nongenomic and genomic steroid actions are responsible for the analgesic and antihyperalgesic effect, where the nongenomic mechanisms lead to the rapid analgesia and antihyperalgesia (minutes) and the genomic mechanisms give a sustained analgesia and antihyperalgesia (hours to days).

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Continuous Preperitoneal Infusion of Ropivacaine Provides Effective Analgesia and Accelerates Recovery after Colorectal Surgery

A Randomized, Double-blind, Placebo-controlled Study

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CME This article and its accompanying editorial have been selected for the ANESTHESIOLOGY CME Program. After reading both articles, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

Background: **Blockade of parietal nociceptive afferents by the use of continuous wound infiltration with local anesthetics may be beneficial in a multimodal approach to postoperative pain management after major surgery. The role of continuous preperitoneal infusion of ropivacaine for pain relief and postoperative recovery after open colorectal resections was evaluated in a randomized, double-blinded, placebo-controlled trial.**

Methods: **After obtaining written informed consents, a multiholed wound catheter was placed by the surgeon in the preperitoneal space at the end of surgery in patients scheduled to undergo elective open colorectal resection by midline incision. They were thereafter randomly assigned to receive through the catheter either 0.2% ropivacaine (10-ml bolus followed by an infusion of 10 ml/h during 48 h) or the same protocol with 0.9% NaCl. In addition, all patients received patient-controlled intravenous morphine analgesia.**

Results: **Twenty-one patients were evaluated in each group. Compared with preperitoneal saline, ropivacaine infusion reduced morphine consumption during the first 72 h and improved pain relief at rest during 12 h and while coughing during 48 h. Sleep quality was also better during the first two postoperative nights. Time to recovery of bowel function (74 ± 19 *vs.* 105 ± 54 h; $P = 0.02$) and duration of hospital stay (115 ± 25 *vs.* 147 ± 53 h; $P = 0.02$) were significantly reduced in the ropivacaine group. Ropivacaine plasma concentrations remained below the level of toxicity. No side effects were observed.**

Conclusions: **Continuous preperitoneal administration of 0.2% ropivacaine at 10 ml/h during 48 h after open colorectal resection reduced morphine consumption, improved pain relief, and accelerated postoperative recovery.**

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LOCAL anesthetic wound infiltration is widely recognized as a useful adjunct in a multimodal approach to postoperative pain management.[1,2] In the setting of major surgery, a single bolus administration of a local anesthetic has a limited effect because of its short duration of action. Prolonged administration through a multiholed catheter positioned by the surgeon at the end of the procedure increases the duration of action and may thereby improve the efficacy of local wound infiltration. This new modality of administration has expanded the indications for parietal infiltrations toward major painful procedures, such as cardiac,[3] thoracic,[4] major gynecologic,[5] breast augmentation,[6] cesarean delivery,[7] or spinal surgery.[8] In all of these cases, continuous wound infiltrations led to pain relief, as well as a reduction in parenteral morphine consumption and in some of the opioid-related side effects, as compared with parenteral morphine-based analgesia alone. A recent systematic review of randomized controlled trials confirmed the benefits and the safety of this technique, showing a very low incidence of complications.[9]

However, the analgesic interest of continuous wound infiltration may vary according to the type of the surgical procedure.[9] For example, the benefit of this technique after open abdominal surgery remains controversial, and current evidence shows either weak or no benefit.[10–12] Among the possible explanations for these disappointing results, the catheter placement must be considered. In previous studies, local anesthetics were delivered subcutaneously, thereby restricting the blockade of parietal nociceptive inputs to the superficial layer of the abdominal wall. However, both fascia of the abdominal muscles

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and peritoneum, which are richly innervated tissues, are also injured by the surgical incision. Incision of the parietal peritoneum is especially likely to contribute to postoperative pain and may be involved in several pathophysiologic repercussions, such as prolonged paralytic ileus. Preliminary reports suggested that infusing local anesthetics in the preperitoneal space, thereby blocking peritoneal afferents, may have a beneficial effect after subcostal incisions for cholecystectomy or splenectomy.[13] Until now, the contribution of peritoneal injury to the overall pain after open colorectal surgery has been markedly underestimated.

In this randomized, double-blind, placebo-controlled study, we aimed to evaluate whether continuous infusion of a local anesthetic over the parietal peritoneum, by a multiholed catheter in the preperitoneal position, *i.e.*, deep in the wound, between the closed peritoneum and the fascia, would have an impact on morphine consumption, pain relief, and recovery after open colorectal surgery.

Materials and Methods

This prospective, randomized, double-blind, placebo-controlled study was approved by the Committee for the Protection of Human Subjects in Biomedical Research. All of the patients signed a written informed consent form. The study was conducted from July 2005 to May 2006. Patients were recruited at St. Antoine Hospital, Paris France (n = 34); Geneva University Hospital, Geneva, Switzerland (n = 13); and Strasbourg University Hospital, Strasbourg, France (n = 2).

Patients included in the study had an American Society of Anesthesiologists physical status I or II, were aged between 18 and 80 yr, and were scheduled to undergo elective open resection of malignant colorectal tumors through a periumbilical midline incision followed by a primary anastomosis. Exclusion criteria were obesity (body mass index > 30 kg/m^2), inflammatory bowel diseases, preoperative cognitive dysfunction, chronic pain, preoperative opioid consumption, psychiatric disorders, inability to use the patient-controlled analgesic device, and *a priori* indication for dysfunctioning stoma or abdominal suction drains.

Anesthetic Technique

Patients were premedicated with oral hydroxyzine (1 mg/kg) given 1 h before the induction of anesthesia. After arrival in the operating room, patients were monitored as usual, and anesthetic induction was performed with intravenous thiopental (3–4 mg/kg), sufentanil (0.2–0.3 μg/kg), and atracurium (0.5 mg/kg). After tracheal intubation, mechanical ventilation was initiated with a mixture of 50% O_2 and 50% N_2O and adjusted to keep end-tidal carbon dioxide tension between 30 and 35 mmHg. Anesthesia was maintained with desflurane or sevoflurane, continuous infusion of atracurium (0.4–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.1–0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$). At the end of the procedure, halogenated agents were switched off, and 100% O_2 was given with 8 l/min fresh gas flow. Residual neuromuscular blockade was reversed, if needed, with a mixture of atropin and neostigmine. A warming forced-air blanket (Bair-Hugger; Arizant Health Care Inc., Eden Prairie, MN) covering the upper part of the body was used routinely to prevent intraoperative hypothermia.

Study Protocol

After arrival in the operating room, patients were randomly allocated to receive a continuous wound infusion of either 0.2% ropivacaine (ropivacaine group) or 0.9% saline (control group). The attending anesthesiologist sent the inclusion number to the pharmacist. The inclusion number referred to a sealed envelope, which was opened by the pharmacist and which contained the patient's allocation group (determined by a computer-generated random list). Randomization was established by blocks of four patients.

The pharmacist prepared a 10-ml syringe for bolus infusion and, at the same time, filled the elastomeric pump (On-Q Pain Buster®, ref. PS12507I; I-Flow Corp., Lake Forest, CA), under aseptic conditions, with 480 ml solution. Both the 10-ml syringe and the elastomeric pump were provided to the treating physician. Only the pharmacist was aware of the code defining the type of solution to be administered. Physicians in charge of the patient, during both intraoperative and postoperative periods, were fully blinded to the patient's group assignment.

At the end of the surgery, after closure of the parietal peritoneal membrane with running sutures, the surgeon inserted a 20-gauge multiholed Soaker catheter (On-Q Pain Buster®, ref. PS12507; I-Flow Corp.) approximately 3 cm from the lower end of the midline incision through an introducer needle. The catheter was positioned between the previously closed parietal peritoneum and the underside of the transversalis fascia, along the full length of the wound (fig. 1). Thereafter, the surgeon closed the fascia layer and skin and secured the infusion catheter to the skin. When the wound was closed, a 10-ml bolus of test solution was administered through the catheter. The prefilled elastomeric pump, set to deliver a 10-ml/h constant rate during 48 h (infusion pressure = 10 psi corresponding to 517 mmHg), was connected immediately thereafter. The catheter was covered with a transparent dressing.

Postoperative Care

Except for the medication delivered through the preperitoneal wound catheter, postoperative management was strictly identical for all patients. Tracheal extubation was performed when the patient was conscious, with a respiratory rate between 12 and 30 breaths/min, with a

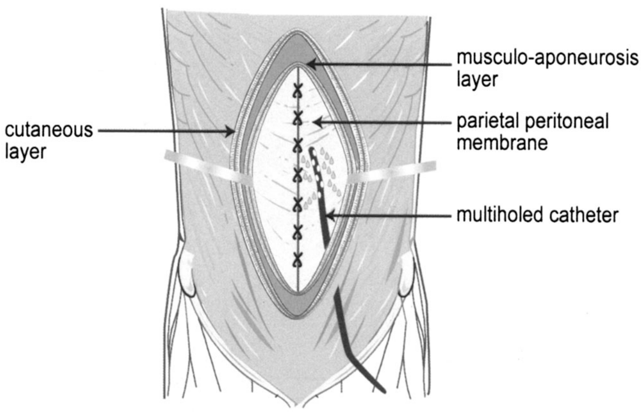

Fig. 1. Schematic representation of the multiholed catheter placed in preperitoneal position.

central core temperature greater than 36°C, and without residual muscle weakness. After tracheal extubation, pain was assessed, and those patients with pain greater than 2 on a 4-point verbal rating scale received intravenous boluses of 2 mg morphine as titration, with 5-min intervals, until pain decreased to a maximum verbal rating scale of 1 (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). A patient-controlled analgesia (PCA) device (Graseby 9300; Watford Herts, United Kingdom) was then connected to an intravenous infusion and set to deliver a 1-mg dose of morphine with a 7-min lockout time. Before surgery, each patient had received information on the PCA device and was able to use it efficiently. PCA was maintained until daily morphine consumption was less than 10 mg.

Nonopioid intravenous analgesics (ketoprofen 50 mg × 3 daily, or acetaminophen 1 g × 4 daily in case of contraindication to non steroidal antiinflammatory drugs) were given as rescue medication if pain was not controlled adequately, as defined by a verbal numerical scale above 4 out of 10 at rest, or at the patient's request for better pain relief despite the morphine PCA.

Nasogastric tube and urinary bladder catheter were left in place for at least 24 h after surgery. Oral fluids were started as soon as the patients passed flatus. Solid meals were given the day after.

Study Parameters

Evaluation started at the end of the wound closure (hour 0 [H0]). At that time, the bolus of test solution was administered.

The primary endpoint was parenteral morphine consumption, which was measured daily on the PCA device.

Secondary outcomes measures were as follows:

- The number of patients requiring morphine titration in the postanesthesia care unit (PACU) and the dose of morphine administered were recorded.
- Pain was measured at rest and at mobilization (defined as pain experienced during coughing) using the verbal numerical scale from 0 (no pain) to 10 (worst pain imaginable) at H2, H6, H12, and thereafter once daily until discharge.
- The modified Aldrete score was used to estimate the time course of initial arousal from anesthesia in the recovery room.[14] After reaching an Aldrete score greater than 8, patients were considered fit for discharge from the PACU to the ward.
- Time to return of gastrointestinal function was defined as the time from the end of surgery (H0) until the first bowel movement. Time until the first occurrence of flatus was noted.
- Mental function was assessed by the Digit Symbol Substitution Test performed daily until patients attained the preoperative score (determined the day before surgery).[15]
- Quality of the night's sleep was evaluated each morning with a 10-cm visual analog scale from 0 (very poor quality of sleep) to 10 (excellent quality of sleep).
- Duration of hospital stay could be considered as a synthetic index of the postoperative recovery. Patients were considered ready for discharge when they fulfilled all of the criteria from an objective scale (see appendix). The criteria were checked for each patient twice daily by a surgeon who was blinded to the patient's group assignment. The duration of hospital stay was therefore assessed to the nearest half-day time interval. Authorization for discharge was rapidly followed by actual hospital discharge.
- All side effects were recorded. The incidence of postoperative nausea or vomiting, requiring specific treatment with intravenous ondansetron (4 mg), was noted. The level of sedation was monitored at H2, H6, H12, H24, and then twice daily with a 4-point rating scale (where 0 = fully alert, 1 = sleepy but easily aroused with verbal stimulation, 2 = sleepy but barely arousable, and 3 = unconscious patient not answering to contact). Special attention was paid to detect any problem with the infusing material.
- To study the diffusion of the local anesthetic in the preperitoneal position, one patient underwent a computer tomography contrast study 24 h after the surgery. A 10-ml mixture of nonionic contrast material and saline solution (1:1) was injected, and transverse and coronal sections were obtained.
- Plasma concentrations of ropivacaine (total and unbound) were measured by chromatography at H24, H48, and H60 in eight patients who were allocated to receive ropivacaine. Those patients were selected during the constitution of the randomization list. The information that blood samples would be needed was notified in the randomization envelopes. To respect the blindness of the study, blood samples were also taken from eight patients allocated to the placebo group. Unbound fraction of ropivacaine was measured in only six patients because the volume of the blood samples after

the dosage of the total fraction was not sufficient in two patients. After pH adjustment by equilibration during 2 h in an agitated water bath with 95% N_2 and 5% CO_2 at 37°C, protein binding was determined using ultrafiltration at 35°C using YMT membranes (Millipore, Saint-Quentin-en-Yvelines, France). In all patients, an electrocardiogram was performed on the first and second postoperative days to document possible ropivacaine cardiac toxicity.

- Patients were contacted by phone between 8 and 12 weeks after the surgery and asked about any residual wound pain and analgesia requirements.

Statistical Analysis

The calculation of the sample size was based on the primary endpoint, *i.e.*, morphine consumption during the first postoperative day. Taking into account retrospective data from our institution, showing a morphine PCA consumption of 50 ± 15 mg in a similar population, a sample size of 21 patients in each group was required to detect as significant a between-group difference of 30%, with an α risk of 0.05 and a β risk of 0.1.

Pain intensity between the two groups was compared with repeated-measures (two-way) analysis of variance, the independent within-subject variable being the time of evaluation and the intersubject variability being the verbal numerical scale values. A two-level between-groups factor was used (ropivacaine, control). In case of statistical differences between the two groups, *post hoc* pairwise comparisons were performed with the Fisher protected least significant difference test (Statview®; Abacus Concepts, Inc., Berkeley, CA).

Because the morphine consumption was not normally distributed after the 48th postoperative hour (high value of the asymmetric test), the between-group comparisons were performed with nonparametric Mann–Whitney test. Other continuous quantitative variables were analyzed with a two-tailed Student *t* test. Categorical data were analyzed using Mann–Whitney test or chi-square contingency table. Logistic regression was performed to test for a possible interaction between the centers of evaluation and the main studied parameter.

Variables are presented as mean ± SD. The threshold for statistical significance was set at $P < 0.05$. Non–statistically significant differences are abbreviated as NS.

Results

Forty-nine patients were enrolled in the study. Three patients were excluded from analysis because of an intraoperative decision to use a dysfunctioning stoma. In one patient (allocated to the saline group), the catheter was withdrawn at H12 because of severe hyperthermia. This episode resolved spontaneously, without any sign

A

B

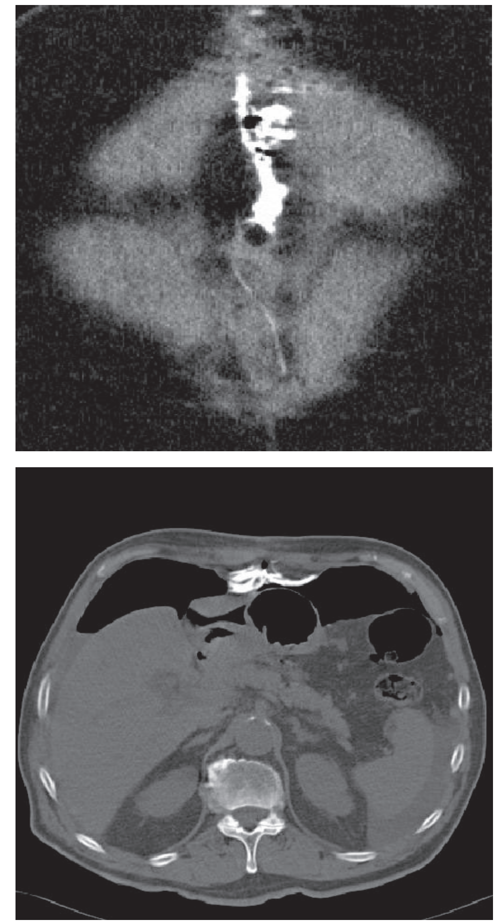

Fig. 2. Contrast-enhanced computer tomography scan obtained by injection of a 10-ml mixture of nonionic contrast material and saline solution (1:1) 24 h after surgery into the preperitoneal wound catheter. (*A*) Coronal section, (*B*) sagittal section.

of local wound infection. Microbiologic culture of the tip of the catheter was sterile. A further 3 patients were excluded because of parietal tumor extension (1 patient), lack of peritoneum (1 patient who had undergone previous major intraabdominal surgery), and intraoperative urologic complication (1 patient). Twenty-one patients successfully completed the study in each groups. Logistic regression did not show any significant interaction between centers of evaluation and the main parameter, *i.e.*, morphine consumption ($P = 0.31$). There were no missing values, except for the pain assessment at 12 h postoperatively because it was overnight and some patients were sleeping (12 patients in both groups).

As demonstrated by computer tomography, once infused in the preperitoneal position, the radiopaque contrast media remained in the deep layer of the abdominal wall, in close vicinity to the peritoneal injury, without any signs of intraabdominal penetration (fig. 2). The local anesthetic spread toward the upper part of the abdominal wall due to the pressure applied when injecting the radiopaque solution. Indeed, pressure to infuse the computer tomography scan contrast was approxi-

Table 1. Demographic and Intraoperative Data

	Ropivacaine (n = 21)	Control (n = 21)	*P* Value
Age, yr	58 ± 10	62 ± 9	0.17
Sex, M/F	14/7	11/10	0.52
Height, cm	171 ± 10	166 ± 10	0.14
Weight, kg	73 ± 14	69 ± 14	0.35
ASA physical status, I/II	11/10	7/14	0.34
Surgical procedure			0.6
Left hemicolectomy	16	13	
Right hemicolectomy	3	5	
Rectal resection	2	3	
Duration of surgery, min	189 ± 42	182 ± 57	0.67
Size of incision, cm	22 ± 5	19 ± 4	0.01
Sufentanil consumption, μg	49 ± 14	54 ± 18	0.27
Volume loading			
Crystalloids, ml	2,147 ± 642	2,131 ± 654	0.93
Colloids, ml	590 ± 202	600 ± 223	0.93

Values are mean ± SD.

ASA = American Society of Anesthesiologists.

mately 10 times higher than the infusion pressure of the elastomeric pump.

Demographic and intraoperative data are presented in table 1. Tracheal extubation was performed 20 ± 9 and 23 ± 10 min after H0, respectively, in the ropivacaine and control groups (NS). In the control group, 20 patients, as compared with 15 patients in the ropivacaine group, needed intravenous morphine titration in the PACU (NS). The total doses of intravenous morphine given as titration in the PACU were 4 ± 3 and 7 ± 5 mg in the ropivacaine and control groups, respectively (P = 0.004). Time to reach an Aldrete score greater than 8 was not different between groups (63 ± 29 and 70 ± 48 min in the ropivacaine and control groups, respectively).

After discharge from the PACU, morphine consumption was significantly reduced in the ropivacaine group as compared with the control group during the first 3 postoperative days (fig. 3). Total morphine consumption over the first 3 postoperative days was 48 ± 23 mg in the ropivacaine group and 84 ± 37 mg in the control group (P = 0.0004).

Pain intensity was significantly reduced in the ropivacaine group compared with control group, both at rest (significant group–time interaction effect on analysis of variance; $P < 0.01$) and during coughing (significant group–time interaction effect on analysis of variance; $P < 0.01$). Pairwise comparisons showed that the difference was significant throughout the first 12 h for pain at rest and throughout the first 48 h for pain during coughing (figs. 4A and B). During the first postoperative day, 6 patients in the ropivacaine group and 11 patients in the control group needed rescue analgesic medications (NS). The same applied to 4 and 7 patients, respectively, during the second postoperative day (NS).

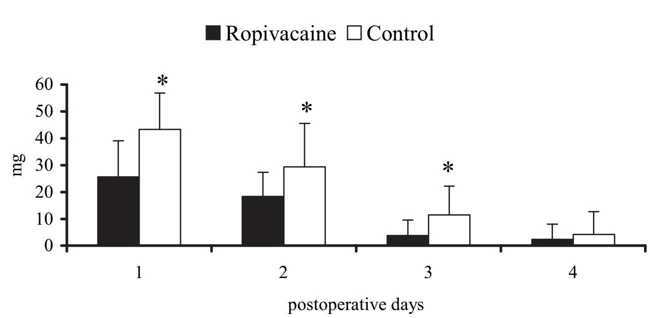

Fig. 3. Daily morphine consumption. * ***P* < 0.05. Results are mean ± SD.**

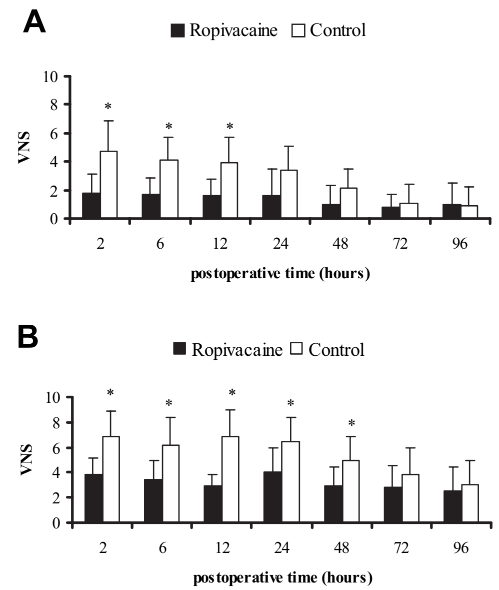

Fig. 4. Pain intensity at rest (*A*) and during coughing (*B*), assessed using a verbal numerical scale (VNS). * ***P* < 0.05. Results are mean ± SD.**

No major adverse event occurred. Two patients in the ropivacaine group and six patients in the control group experienced severe postoperative nausea or vomiting requiring treatment (NS). The course of postoperative recovery is presented in table 2. Quality of sleep was rated as better in the ropivacaine group than in the control group during the two first postoperative nights. Time to recover preoperative mental status, assessed by Digit Symbol Substitution Test, was similar between the two groups. Recovery of intestinal transit, assessed by the time to first bowel movement, was faster in the ropivacaine than in the control group (P = 0.02), as well as the time to be eligible for discharge from the hospital (P = 0.02).

Total plasma concentrations of ropivacaine were 2.3 ± 0.9, 1.6 ± 0.9, and 0.4 ± 0.3 μg/ml, respectively, at H24, H48, and H60. Plasma unbound fractions of ropivacaine are given in figure 5. Unbound fractions were below the quantification threshold (0.01 μg/ml) at H60 for all patients except one (0.03 μg/ml).

At the follow-up evaluation, between 8 and 12 weeks after the surgery, one patient in each group reported residual wound pain requiring analgesic medications.

Table 2. Side Effects and Recovery Parameters

	Ropivacaine (n = 21)	Control (n = 21)	*P* Value
Sleep quality during first night, cm	7.9 ± 1.6	5.0 ± 3.2	< 0.001
Sleep quality during second night, cm	8.6 ± 1.2	6.9 ± 2.4	< 0.001
Time to recover preoperative DSST, days	3.1 ± 1.1	3.0 ± 1.4	0.8
Time to first flatus, h	54 ± 16	72 ± 41	0.06
Time to first feces, h	74 ± 19	105 ± 54	0.02
Duration of hospital stay, h	115 ± 25	147 ± 53	0.02

Values are mean ± SD.

DSST = Digit Symbol Substitution Test.

Discussion

The increasing use of wound infiltration of local anesthetics as part of multimodal analgesia after major surgery is based on the recognition of the important role played by parietal nociceptive afferents in the overall pain and in the pathophysiologic repercussions induced by surgery. In this study, we provide for the first time evidence that continuous infusion of ropivacaine into the preperitoneal space for 48 h has a beneficial effect on pain relief, reduces the parenteral morphine consumption, and accelerates the recovery after open colorectal resection, as compared with parenteral analgesia alone.

Open colorectal surgery induces severe and prolonged postoperative pain, especially during mobilization.[16] Systemic or even epidural opiates are not effective enough to fully control pain induced by mobilization.[17] Only epidural local anesthetics have shown a marked benefit in controlling pain at mobilization.[18] When compared with systemic patient-controlled morphine analgesia, epidural analgesia using local anesthetic is significantly better for pain control during mobilization for the first 2 postoperative days after open colonic resection.[17] However, several medical conditions preclude the use of epidural analgesia, and approximately 20–30% of eligible patients do not benefit from it because of technical problems or failure in efficiency.[19,20] These limitations have stimulated the search for alternative ways of pain management in the setting of abdominal laparotomy.

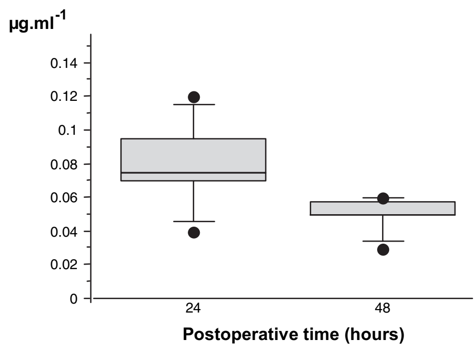

Fig. 5. Unbound plasma concentration of ropivacaine at hours 24 and 48. Dosages obtained from six patients. Unbound fractions were below the quantification threshold (0.01 µg/ml) at hour 60 for all patients except one (0.03 µg/ml). Results in median interquartile range (*gray box*), 90% confidence interval and extreme values (*black dots*).

In the current study, we show that continuous preperitoneal infiltration of ropivacaine exhibits a significant benefit over systemic analgesia alone, both on pain at rest and at mobilization. Pain at mobilization was significantly better alleviated throughout the first 48 postoperative hours, corresponding to the duration of the local anesthetic infusion. It is noteworthy that pain intensity did not increase after finishing the local anesthetic infusion. Moreover, daily morphine consumption was still significantly less in the ropivacaine group than in the control group during the 24 h after catheter removal. This is in accordance with some recent data suggesting that the blockade of parietal afferents may reduce spinal dorsal horn neuron sensitization, thereby providing postoperative analgesic effect that may outlast the duration of the wound infusion.[21] In the current study, there was only one patient in each group with residual long-term wound pain. However, this information was collected by phone interview using simple questions and without clinical examination. This result might have been different if a more detailed questionnaire about the nature and the intensity of the pain had been proposed and if a clinical examination had been performed. Furthermore, it cannot be excluded that other nonpharmacologic parameters, related to the infusion, may have played a role in reducing dorsal horn neuron sensitization and the incidence of long-term postoperative pain in both groups.

The current results emphasize that the peritoneum and the deep muscular layer play a crucial role in the pain induced by abdominal incisions. This assumption is further supported by the failure of epidural analgesia when metameric level is not high enough to block peritoneal nociceptive influx, even after lower abdominal surgery.[22] Furthermore, recent data from animal studies have shown that parietal pain may sensitize neurons in the spinal cord to visceral colonic pain.[23] Therefore, it cannot be excluded that blockade of parietal pain influx may even contribute to a reduction of the visceral component of pain.

Injection of radiopaque contrast media through a preperitoneal wound catheter shows that once injected, the local anesthetic remains in close vicinity of the abdominal wound incision, between the injured parietal peritoneum and the muscular layer, thereby effectively blocking peritoneal afferents. Information drawn from computer tomography must be taken with caution because there was only one case and the diffusion of the radiopaque media may not reflect the exact diffusion of the local anesthetic.

When limited to the subcutaneous layers, local anesthetic wound infusion has been disappointing after laparotomy. Cheong *et al.*[11] infused 0.5% bupivacaine at a flow rate of 2 ml/h for 60 h into the subcutaneous layer of a left iliac fossa incision. Only pain at rest, not during movement, was better controlled in patients allocated to receive local infusion during the first postoperative day, and total morphine consumption was reduced only moderately. Fredman *et al.*[10] did not show any benefit for pain relief or for morphine consumption when infusing 0.25% bupivacaine into the subcutaneous space by PCA device set to deliver 9 ml with a 60-min lockout interval, during 24 h after abdominal laparotomy. More recently, Baig *et al.*[12] presented results obtained by continuous subcutaneous infusion of 0.5% bupivacaine at 4 ml/h for 72 h and showed a significant reduction in daily morphine consumption but no difference in overall postoperative pain. These results underline the limited influence of the superficial layer of the abdominal wall on overall postoperative pain after laparotomy.

Ropivacaine and bupivacaine have been the most used local anesthetics for continuous wound infiltration.[9] In this indication, and at similar doses, analgesic efficacy between these two agents seems comparable.[24] In the current study, we chose ropivacaine instead of bupivacaine because of its lower systemic toxicity and its shorter elimination half-life, reducing the risk of plasma accumulation during prolonged infusion.[25] The dose/volume infused was chosen according to the study by Burm *et al.*[26] showing that a constant rate (10 ml/h) epidural infusion of 0.2% ropivacaine for 72 h after major orthopedic surgery was well tolerated and associated with plasma concentrations below the level of toxicity. In the current study, total and unbound fractions of ropivacaine were comparable to those obtained in the study by Burm *et al.*[26] No sign or symptom indicative of systemic toxicity was noted. Both unbound and total fraction of ropivacaine decreased between the 24th and 48th postoperative hours, showing the absence of drug accumulation. The highest unbound ropivacaine concentration after 24 h of infusion was 0.12 μg/ml, which is slightly above the threshold concentration for mild central nervous system toxicity derived after rapid intravenous infusion of ropivacaine in healthy subjects.[27] This suggests a sufficient margin of safety with the use of the studied infusion regimen, but cautions against using higher ropivacaine doses in this setting.

None of the studies on subcutaneous local anesthetic wound infusion reported any positive influence on postoperative recovery. In contrast, we showed that preperitoneal wound infusion of ropivacaine improved sleep quality during the first two postoperative nights, reduced the duration of paralytic ileus, and shortened the duration of hospital stay. Time to ileus resolution after abdominal surgery is one of the most important factors contributing to the duration of hospital stay. Mechanisms whereby preperitoneal continuous administration of a local anesthetic reduce the duration of ileus may include improvement of analgesia, with concomitant reduction in sympathetic activation, and morphine sparing. However, because some experimental studies suggest that the afferent limb of the reflex leading to a postoperative ileus originates primarily from the peritoneum, it cannot be excluded that a direct effect of local anesthetics on the peritoneal membrane may be directly implicated.[28] Furthermore, as hypothesized with epidural analgesia, systemic effects of local anesthetics, which are known to have antiinflammatory property, may also speed up the return of bowel function,[29] although this remains under debate.[30] In addition to the effect on ileus resolution, it has been recently shown in an animal study that wound infiltration with local anesthetics may partly restore food intake behavior, which is disturbed after an abdominal wall incision.[31] This point may have significant implications for postoperative recovery but must be evaluated in the human setting.

Sleep quality is important for patients' comfort and postoperative fatigue. The better sleep quality in patients who received a preperitoneal ropivacaine infusion may be associated with more vigor and contribute to a faster rate of recovery in this subgroup. It may be due to better pain relief but also to a reduction in morphine consumption, because opiates are known to disrupt sleep quality.[32] Finally, we chose to evaluate the duration of hospital stay because it represents a synthetic index of recovery. To ensure reliable assessment, an objective scale was used. Continuous preperitoneal infusion of ropivacaine reduced the duration of hospital stay on average by more than 24 h, and it may therefore be considered to be among the analgesic techniques that have proven a benefit for postoperative rehabilitation after abdominal surgery. Potential economical benefits should be evaluated in further studies.

Preperitoneal continuous infusion seems to be well tolerated and devoid of unwanted side effects. In agreement with other reports on continuous local anesthetic wound perfusion, no local complications were observed. In the metaanalysis by Liu *et al.*,[9] the overall wound infection rates were similar between catheter with local anesthetic (0.7%) and catheter with placebo or no-catheter control group (1.2%). The incidence of reported catheter or pump failure was 1.1%.[9] In the current study, no technical problems occurred with the infusion devices. However, larger sample sizes must be evaluated before a definite conclusion can be drawn about the safety of this technique.

The current study reports encouraging results with the use of a continuous infusion of 0.2% ropivacaine at 10 ml/h during 48 h, but further questions will have to be answered in the future, such as the choice of local anesthetic, the optimal dose/volume per time, and the influence of the mode of administration (*e.g.*, patient-controlled administration) on efficiency. Nonetheless, several limitations of this analgesic technique should be mentioned, such as patients with dysfunctioning stoma, not accessible to local wound perfusion, and those with previous abdominal surgery including peritoneal resection.

Several secondary evaluation parameters, such as the incidence of postoperative nausea or vomiting, or the number of patients who have required rescue analgesic medications, showed a trend in favor of the ropivacaine-group treatment without reaching the threshold of statistical significance. This is probably in relation with the small sample size which had been calculated based on the primary outcome.

In conclusion, preperitoneal continuous infiltration of 0.2% ropivacaine at 10 ml/h during 48 h seems to be an effective method to relieve pain after open colorectal surgery. It reduced morphine consumption and accelerated the postoperative recovery. It is easy to implement and seems devoid of major side effects, making specific supervision unnecessary. It could therefore be considered as an interesting alternative to epidural analgesia in this setting.

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Appendix: Criteria for Hospital Discharge

- Apyrexia defined as central core temperature between 36.7° and 37.8°C
- Leukocyte count less than 12×10^9/l
- Absence of anemia with clinical repercussion (no dyspnea at rest, no orthostatic hypotension)
- Resumption of normal bowel function (bowel movement without diarrhea)
- Lack of nausea and/or vomiting
- Lack of significant pain (verbal rating scale < 2 at movement)
- Ability to wake up and ambulate without help