Intravenous Lidocaine Infusion Facilitates Acute Rehabilitation after Laparoscopic Colectomy

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Background: Intravenous infusion of lidocaine decreases postoperative pain and speeds the return of bowel function. The authors therefore tested the hypothesis that perioperative lidocaine infusion facilitates acute rehabilitation protocol in patients undergoing laparoscopic colectomy.

Methods: Forty patients scheduled to undergo laparoscopic colectomy were randomly allocated to receive intravenous lidocaine (bolus injection of 1.5 mg/kg lidocaine at induction of anesthesia, then a continuous infusion of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ intraoperatively and $1.33 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 24 h postoperatively) or an equal volume of saline. All patients received similar intensive postoperative rehabilitation. Postoperative pain scores, opioid consumption, and fatigue scores were measured. Times to first flatus, defecation, and hospital discharge were recorded. Postoperative endocrine (cortisol and catecholamines) and metabolic (leukocytes, C-reactive protein, and glucose) responses were measured for 48 h. Data (presented as median [25–75% interquartile range], lidocaine *vs.* saline groups) were analyzed using Mann–Whitney tests. $P < 0.05$ was considered statistically significant.

Results: Patient demographics were similar in the two groups. Times to first flatus (17 [11–24] *vs.* 28 [25–33] h; $P < 0.001$), defecation (28 [24–37] *vs.* 51 [41–70] h; $P = 0.001$), and hospital discharge (2 [2–3] *vs.* 3 [3–4] days; $P = 0.001$) were significantly shorter in patients who received lidocaine. Lidocaine significantly reduced opioid consumption (8 [5–18] *vs.* 22 [14–36] mg; $P = 0.005$) and postoperative pain and fatigue scores. In contrast, endocrine and metabolic responses were similar in the two groups.

Conclusions: Intravenous lidocaine improves postoperative analgesia, fatigue, and bowel function after laparoscopic colectomy. These benefits are associated with a significant reduction in hospital stay.

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OVER the past decade, the concept of fast-track surgery has been developed to reduce postoperative morbidity and duration of hospitalization, and to accelerate postoperative recovery and convalescence.[1–3] Acute rehabilitation programs combine preoperative optimization of patients' physical and psychological status, attenuation of surgical stress, dynamic pain relief, enforced mobilization, and early oral (enteral) nutrition, as well as changes in surgical care de-emphasizing tubes and drains. This multimodal approach to enhanced postoperative recovery has been largely developed and used for abdominal operations, especially colon surgery.[4–7] Many of these pathways involve comprehensive clinical approaches; however, the relative contributions of individual components to the overall success have yet to be evaluated.

Effective postoperative analgesia is key to acute rehabilitation. Epidural analgesia using local anesthetic seems particularly appropriate after abdominal surgery because it reduces surgical stress,[8] provides excellent dynamic pain relief allowing enforced mobilization,[9,10] and improves gastrointestinal function.[11,12] Epidural analgesia is therefore included in multimodal approaches for both open and laparoscopic colon resection.[4,5,13] However, the benefits of epidural analgesia for minimally invasive laparoscopic colectomy have been questioned in several randomized trials.[14,15] Furthermore, insertion of epidural catheters carries some risk, is at times contraindicated, and may be declined by the patient.

An alternative approach to accelerate postoperative recovery after colon surgery is administration of intravenous lidocaine, which has analgesic,[16,17] antihyperalgesic,[17–19] and antiinflammatory[20] properties and has been reported to speed the return of bowel function after surgery.[16,21] In a case series, acute rehabilitation after laparoscopic colectomy using intravenous lidocaine yielded outcomes similar to those reported using epidural analgesia.[22] Furthermore, nontoxic plasma lidocaine concentrations reduce requirements for various volatile anesthetics in several animal species[23–25]—although the benefits in humans remain unclear.[26–28] Finally, intravenous lidocaine is inexpensive, easy to administer, and relatively safe. It is thus an attractive intervention with wide potential applicability. We therefore tested the hypothesis that systemic lidocaine facilitates acute rehabilitation after laparoscopic colectomy.

Materials and Methods

With approval of the Institutional Ethics Committee of Centre Hospitalier Universitaire de Liège (Liège, Belgium) and written informed consent from each patient, we enrolled 45 American Society of Anesthesiologists physical status I–III patients scheduled to undergo elective laparoscopic colectomy for nonmalignant disease at the Centre Hospitalier Universitaire de Liège. Patients were enrolled from January 2003 until December 2004. Exclusion criteria were age greater than 70 yr, history of gastroduodenal peptic ulcer or renal failure (contraindications to the use of nonsteroidal antiinflammatory drugs), hepatic insufficiency, psychiatric disorder, steroid treatment, or chronic treatment with opioid. Two of the authors (A.K. and J.L.J.) enrolled all of the patients. Fifty-eight patients were assessed for eligibility, but of these, 13 were excluded from participation in the study: 9 patients met exclusion criteria, and 4 declined to participate.

Protocol

Patients fasted at least 6 h and were orally premedicated with 50 mg hydroxyzine and 0.5 mg alprazolam 2 h before surgery. Lactated Ringer's solution (8 ml · kg^{-1} · h^{-1}) was infused throughout surgery.

Anesthesia

Patients were randomly allocated to two groups based on computer-generated codes that were maintained in sequentially numbered opaque envelopes. Allocation envelopes were opened by a pharmacy staff member who then prepared either 2% lidocaine or saline in coded 50-ml syringes. The anesthesiologist in charge of the case was unaware of the patient's group assignment; the study was thus fully double blinded. Just before induction of anesthesia, patients assigned to receive lidocaine (n = 22) were given an intravenous bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion of 2 mg · kg^{-1} · h^{-1}. The lidocaine infusion was continued at a rate of 1.33 mg · kg^{-1} · h^{-1} for 24 h postoperatively. For safety reasons, the lidocaine infusion was connected to the distal part of the intravenous line to avoid accidental bolus administration. Patients assigned to the control group (n = 23) were given equal volumes of saline.

General anesthesia was induced with 0.15 µg/kg sufentanil and 2 mg/kg propofol. Sufentanil was administered before lidocaine to mask potential neurologic side effects secondary to the bolus injection of lidocaine and keep the anesthesiologist blind as to patient's group assignment. Orotracheal intubation was facilitated with cis-atracurium, and cis-atracurium was also used for intraoperative muscle relaxation; full muscle relaxation (no response to train-of-four stimulation) was maintained during surgery (NMT, Datex-Ohmeda S/5 monitor; Datex-Ohmeda, Helsinki, Finland). Anesthesia was maintained with sevoflurane in a mixture of 80% oxygen and air using a semiclosed circuit with 2 l/min fresh gas flow.

Sevoflurane concentration was adjusted to maintain mean arterial pressure within 15% of the preinduction value. The use of opioid was restricted during surgery: Sufentanil, 5 µg, was injected only if mean arterial pressure increased more than 15% or if heart rate was greater than 100 beats/min despite the administration of sevoflurane to an end-tidal concentration of 3.5%. We decided to titrate sevoflurane to hemodynamic endpoints even if these autonomic responses may be less reliable indicators of hypnotic depth than the Bispectral Index of the encephalogram (BIS), because we were concerned that sevoflurane titrated using BIS alone might provide hypnosis but insufficient analgesia. BIS was, nevertheless, monitored (BIS® A-2000 monitor, averaging time = 30 s; Aspect Medical Systems, Newton, MA), and the protocol allowed increases in inspired sevoflurane concentration if BIS exceeded 50. Core temperature was kept above 36.0°C using a forced-air warming system.

All patients were given 0.625 mg droperidol and 2 mg tropisetron, a 5-hydroxytryptamine type 3 antagonist, as prophylaxis against postoperative nausea and vomiting 1 h before the end of surgery.

Surgical Procedure

Two experienced laparoscopic surgeons (B.J.D., S.R.L.) performed procedures using a standard four- or five-trocar technique. For right colectomy, after intracorporeal dissection of the ascending colon and the Bauhin valve, the specimen was exteriorized through a 5- to 6-cm minilaparotomy in the right lower abdomen. After resection of the pathologic colon, the anastomosis was hand-sewn and returned to the abdominal cavity. The minilaparotomy was then closed.

In laparoscopic sigmoid colectomy, the sigmoid colon was first mobilized intracorporeally up to the rectosigmoid junction. The rectosigmoid junction was cut using a stapler. The sigmoid colon was retrieved through a 5- to 6-cm minilaparotomy in the left lower abdomen and then resected. The anvil of a circular stapling device was inserted extracorporeally into the descending colon. After closure of the laparotomy, the pneumoperitoneum was reestablished, and a transanal colorectal anastomosis was completed with a "double-stapling" technique. The surgeons were unaware of the patient's group assignment.

Postoperative Analgesia

Postoperative analgesia was provided in both groups by the combination of the paracetamol (acetaminophen) precursor propacetamol (Pro-Dafalgan®; UPSA Medica, Waterloo, Belgium; 2 g propacetamol = 1 g paracetamol), 2 g intravenously 30 min before the end of surgery and then every 6 h, and ketorolac, 30 mg intravenously every 8 h. Patient-controlled analgesia with piritramide

(Dipidolor®; Janssen Pharmaceutica, Beerse, Belgium), a synthetic opioid, was used as rescue medication (bolus = 1 mg, lockout interval = 5 min, no basal infusion).

Twenty-four hours after the end of surgery, the intravenous infusion of lidocaine or placebo was stopped, and analgesia was provided with oral paracetamol, 1 g every 6 h; diclofenac (a nonsteroidal antiinflammatory drug), 75 mg twice daily; and 100 mg tramadol, if necessary.

Acute Rehabilitation

Gastrointestinal tubes were removed at the end of surgery after aspiration of gastric content. An abdominal drain was left in contact with the anastomosis for 24 h. The bladder catheter was removed on the first postoperative morning.

An intravenous infusion of 5% glucose was started after surgery at a rate of 80 ml/h. Patients were allowed to drink water 6 h after surgery. If patients did not report nausea or vomiting, they were given 200 ml of nutritive supplement without residue (Clinutren® 1.5 kcal/ml; Nestlé, Marne la Vallée, France) 1 h later. On the first postoperative day, patients had a light breakfast and lunch. If this food was tolerated, the intravenous infusion was stopped and a normal diet was resumed. Patients were asked to drink three 200-ml cartons of nutritive supplement each day.

Active mobilization was started in bed 4 h after surgery. Assisted ambulation was enforced on the subsequent days: 20 m in the morning and 50 m in the afternoon on postoperative day 1, then 100 m in the morning and the afternoon on day 2.

All patients received precise oral and written information about our acute rehabilitation program and the importance of their contribution to the early postoperative nutrition and mobilization. Defecation and tolerance of normal diet were required before discharge. Otherwise, patients left the hospital when they felt ready to go home.

Measurements

Arterial pressure, heart rate, and end-tidal sevoflurane concentrations were measured on a Datex-Ohmeda S/5 monitor every 15 min during anesthesia. BIS scores were also recorded at 15-min intervals.

After surgery, piritramide consumption was recorded every 4 h. Pain scores were obtained on a 100-mm visual analog scale at rest, during mobilization from the supine to the sitting position, and during coughing at 2 and 6 h postoperatively and at 9:00 AM, 1:00 PM, and 5:00 PM on postoperative days 1 and 2. Postoperative fatigue scores and gastrointestinal discomfort (colic, abdominal fullness, internal discomfort) were also assessed on a 100-mm visual analog scale at the same times. Times to first flatus, defecation, and hospital discharge were recorded. Patients were instructed and reminded three times a day (at each pain assessment) to record the exact time they passed their first flatus and had their first bowel movement. Episodes of postoperative nausea and vomiting were noted. The clinical personnel recording these data were not aware of the patient's group assignment.

Immediately after induction of anesthesia, the bladder was catheterized and emptied. In the first 30 patients (n = 15 in each group), urine was then collected to measure urinary secretion of cortisol, epinephrine, and norepinephrine to assess the stress response during anesthesia and surgery. Blood samples were drawn in the same patients before surgery and after surgery at 2, 6, 24, and 48 h. Plasma concentrations of glucose, C-reactive protein, cortisol, catecholamines, and leukocyte counts were measured. Cortisol concentrations were determined by radioimmunoassay (Radim, Liège, Belgium). Epinephrine and norepinephrine were measured using high-performance liquid chromatography technique with electrochemical detection. The sensitivity of these two assays was 3 pg/ml; intraassay and interassay coefficients of variation were 7.4% and 9.8%, respectively.

Blood samples were drawn at 5, 15, and 60 min after anesthetic induction, at the end of surgery, and 24 h after the end of surgery to measure plasma lidocaine concentrations using the TDx/TDxFLx Lidocaine Assay System (Abbott Laboratories, Abbott Park, IL; coefficient of variation of less than 5% with controls of 1.5, 3.0, and 7.5 μg/ml).

Statistical Analysis

Because bowel function is the major objective limiting factor for hospital discharge, our sample size was based on anticipated time for recovery of bowel gastrointestinal function (flatus and defecation). A previous study at our institution using a similar protocol[22] indicated that 18 patients per group allowed detecting a 12-h difference in the recovery of bowel function between the groups, at an α level of 0.05 and with 80% power. We therefore enrolled patients until 40 patients (n = 20 in each group) completed the study.

Continuous variables are presented as mean ± SD; they were compared using analysis of variance for repeated measures for two criteria (time and treatment) followed by the Scheffé test for multiple comparisons or the Student t test, as appropriate. If the Kolmogorov-Smirnov normality test did not demonstrate gaussian distributions, the Mann–Whitney test was used; data are then presented as median [25–75% interquartile range]. Categorical data were analyzed with chi-square tests. $P \leq 0.05$ was considered significant.

Results

Demographic data and types and duration of surgery were similar between the two groups, as were indica-

Table 1. Patient Data

	Saline (n = 20)	Lidocaine (n = 20)
Sex, M/F	11/9	15/5
Age, yr	52 ± 13	57 ± 17
Height, cm	170 ± 11	174 ± 9
Weight, kg	73 ± 20	77 ± 11
Type of surgery		
Right/left colectomy	6/14	3/17
Inflammatory bowel disease/polyp resection/dolichosigmoid/diverticulitis*	4/5/0/11	1/3/2/14
Duration of anesthesia, min	170 ± 48	169 ± 47
ASA physical status, I/II/III	7/12/1	7/10/3

Data are presented as mean ± SD or number of patients.

* Indications for laparoscopic colectomy. There were no statistically significant differences between the lidocaine and saline groups.

ASA = American Society of Anesthesiologists.

Table 2. Piritramide Consumption (in Milligrams)

Hours after Surgery	Saline	Lidocaine	P Value
0–2	8 [4–11]	2 [0–5]	0.002
2–6	3 [0–9]	2 [1–3]	0.46
6–20	7 [4–16]	3 [2–9]	0.06
20–24	6 [3–7]	1 [0–1]	< 0.001
0–24	22 [14–36]	8 [5–18]	0.005

Patient-controlled analgesia with piritramide, a synthetic opiate, was used as rescue analgesic during the first 24 h postoperatively. Data are presented as median [25–75% interquartile range].

tions for colectomy (table 1). Of the 45 patients enrolled, 5 patients (3 in the control group and 2 in the lidocaine group) were eliminated from the study because the surgeon decided to convert their surgeries to laparotomies due to surgical problems. Forty patients (n = 20 in each group) completed the study; data from these patients were used in the analysis.

Intravenous lidocaine resulted in a 35% reduction in sevoflurane end-tidal concentration required to maintain hemodynamic stability ($P < 0.001$; fig. 1). The difference between the groups in sevoflurane requirements increased over time (significant interaction between time and treatment effects; analysis of variance, $P < 0.001$). Furthermore, the total dose of sufentanil given to patients in the lidocaine group was significantly less compared with the placebo group: 16.3 ± 3.6 μg (saline) *versus* 13.0 ± 3.7 μg (lidocaine) ($P = 0.008$). Despite a decreased sevoflurane and sufentanil consumption, averaged mean arterial pressure and heart rate were slightly lower in the lidocaine group: 91 ± 7 *versus* 85 ± 6 mmHg ($P = 0.030$) and 69 ± 4 *versus* 63 ± 4 beats/

min ($P = 0.002$), respectively. BIS scores were similar in the two groups: 45.8 ± 0.8 for the saline and 44.6 ± 2.9 for the lidocaine group ($P = 0.20$).

Intravenous lidocaine decreased piritramide consumption during the first 24 h after surgery by more than 50% ($P = 0.005$; table 2). Three patients in the control group, but none in the lidocaine group, requested tramadol after the interruption of piritramide patient-controlled analgesia between the 24th and 48th postoperative hours: These patients were given 100, 200, and 400 mg. Furthermore, patients in the lidocaine group reported less pain during mobilization ($P = 0.020$) and when coughing ($P = 0.010$), and less abdominal discomfort ($P < 0.001$) than patients in the control group (figs. 2 and 3). Pain at rest was not affected significantly ($P = 0.07$). Postoperative fatigue was significantly less ($P = 0.025$) in the lidocaine group than in the control group (fig. 4).

Postoperative recovery of bowel function was significantly accelerated (approximately 12 h for first flatus and approximately 24 h for defecation; $P = 0.001$) and hospital stay was significantly shortened (approximately 1 day; $P = 0.001$) in the lidocaine group (table 3). All
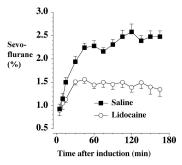

Fig. 1. End-tidal concentration of sevoflurane in 40 patients during laparoscopic colectomy. Half of the patients received intravenous lidocaine (an intravenous bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion of 2 mg · kg^{-1} · h^{-1}); the other half received an equal volume of saline (saline). The sevoflurane concentration in the lidocaine group was significantly lower than in the placebo group (analysis of variance, $P < 0.001$). Data are presented as mean ± SEM. The differences between the two groups were statistically significant. $P < 0.01$ at 15 and 30 min, and $P < 0.001$ after 30 min.
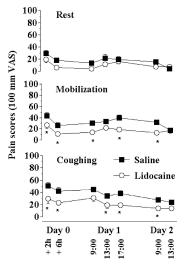

Fig. 2. Self-reported pain scores at 2 and 6 h after surgery, at 9 AM, 1 PM, and 5 PM on the first day after surgery, and at 9 AM and 1 PM on the second day after surgery. Reports were taken with the patients at rest, during mobilization from the supine to the sitting position, and while coughing. Pain was reported on a 100-mm visual analog scale (VAS), with 0 mm being no pain and 100 mm being the worst pain imaginable. Error bars smaller than the data points are not shown. * $P < 0.05$ as compared with saline.
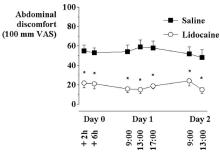
Fig. 3. Self-reported abdominal comfort scores at 2 and 6 h after surgery, at 9 AM, 1 PM, and 5 PM on the first day after surgery, and at 9 AM and 1 PM on the second day after surgery. Abdominal discomfort was reported on a 100-mm visual analog scale (VAS), with 0 mm being no discomfort and 100 mm being the worst imaginable discomfort. * P < 0.05 as compared with saline.

patients in the lidocaine group tolerated a normal diet the day after surgery and had their intravenous infusion interrupted 24 h after surgery, whereas three patients in the control group required prolongation of postoperative fasting and intravenous infusion (31, 54, and 72 h) (P = 0.22). Four patients in the saline group but only one in the lidocaine group experienced nausea (P = 0.17). Vomiting occurred in two patients in the saline group and none in the lidocaine group (P = 0.23)

Urinary epinephrine (8.5 ± 4.4 vs. 9.8 ± 10 μg), norepinephrine (19.1 + 19.0 vs. 15.6 ± 21.8 μg), and cortisol (198 ± 183 vs. 281 ± 178 μg) (control vs.. lidocaine) release during surgery did not differ significantly between the saline and the lidocaine groups. Plasma concentrations of glucose, C-reactive protein, cortisol, epinephrine, and norepinephrine, as well as the leukocyte count, were similar in the two groups (table 4). Lidocaine plasma concentrations were measured in 15 patients and were 1.6 ± 0.9 μg/ml at 5 min, 1.3 ± 0.4 μg/ml at 15 min, and 1.8 ± 0.5 μg/ml at 60 min after the bolus injection of lidocaine; 2.4 ± 0.6 μg/ml at the end of surgery; and 2.7 ± 1.1 μg/ml at the end of the 24-h infusion. The highest plasma concentrations of lidocaine measured at each of these time points were 3.5, 2.1, 2.6, 4.0, and 4.6 μg/ml, respectively.
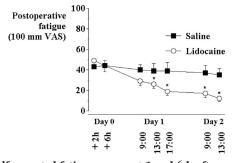

Fig. 4. Self-reported fatigue scores at 2 and 6 h after surgery, at 9 AM, 1 PM, and 5 PM on the first day after surgery, and at 9 AM and 1 PM on the second day after surgery. Fatigue was reported on a 100-mm visual analog scale (VAS), with 0 mm being no fatigue and 100 mm being the worst imaginable fatigue. * P < 0.05 as compared with saline.

Table 3. Bowel Function and Duration of Hospitalization

	Saline	Lidocaine	P Value
First Flatus (hours)	28 [25–33]	17 [11–24]	< 0.001
Defecation (hours)	51 [41–70]	28 [24–37]	0.001
Hospital stay (days)	3 [3–4]	2 [2–3]	0.001

Data are presented as median [25–75% interquartile range].

Discussion

This study demonstrated that perioperative intravenous infusion of nontoxic doses of lidocaine improved postoperative analgesia, reduced postoperative opioid requirements, accelerated postoperative recovery of bowel function, attenuated postoperative fatigue, reduced the duration of hospitalization, and facilitated acute rehabilitation in patients undergoing laparoscopic abdominal surgery. Our results further indicated that moderate plasma lidocaine concentrations reduced sevoflurane requirements necessary for maintaining intraoperative hemodynamic stability and anesthetic depth.

Intravenous lidocaine is analgesic, antihyperalgesic, and antiinflammatory.[16-18,20] These properties are mediated by a variety of mechanisms, including sodium channel blockade,[20] as well as inhibition of G protein–coupled receptors[20,29] and N-methyl-D-aspartate receptors.[30,31] In this study, intravenous lidocaine reduced postoperative opioid consumption, as well as pain scores during activity. Interestingly, the analgesic effect persisted after the lidocaine infusion was discontinued, which suggests a prevention of spinal or peripheral hypersensitivity or both. Inhibition of N-methyl-D-aspartate receptors,[30,31] which play a major role in postoperative hyperalgesia,[32,33] polymorphonuclear leukocyte priming,[34] or both may play a role in this effect. Abdominal discomfort was significantly reduced by lidocaine, which is consistent with the ability of lidocaine to alleviate visceral pain in animal models.[35]

We note that the analgesic effects of intravenous lidocaine were readily observed despite the postoperative administration of paracetamol and a nonsteroidal antiinflammatory drug, each of which reduces postoperative opioid consumption and pain scores during mobilization.[36-38] The analgesic effect of lidocaine might thus have been even greater in the absence of these nonopioid analgesics. Postoperative fatigue was significantly reduced, not only during the lidocaine infusion, but also after its interruption. The improved postoperative analgesia and the reduced opioid consumption may have contributed to this beneficial action. Reduced fatigue may also be related to the subjective sense of heightened alertness reported by normal volunteers during infusion of local anesthetics.[39]

As expected from previous reports,[23,40,41] lidocaine affected neither the intraoperative and postoperative stress response nor the metabolic responses. On one hand, this suggests that inhibition of the stress response requires

Table 4. Endocrine and Metabolic Response after Laparoscopic Colectomy

	Preop	+2 h	+6 h	+24 h	+48 h
Cortisol, nm					
Saline	428 ± 36	599 ± 47	436 ± 61	298 ± 47	348 ± 55
Lidocaine	389 ± 47	483 ± 52	353 ± 58	337 ± 47	337 ± 28
Epinephrine, pm					
Saline	185 ± 33	339 ± 44	218 ± 55	213 ± 16	207 ± 16
Lidocaine	289 ± 44	311 ± 38	295 ± 33	289 ± 60	235 ± 27
Norepinephrine, pm					
Saline	1,986 ± 292	2,435 ± 353	2,294 ± 928	2,053 ± 381	1,867 ± 297
Lidocaine	2,222 ± 297	2,569 ± 370	1,834 ± 281	1,896 ± 236	1,632 ± 219
Glucose, mm					
Saline	6.1 ± 0.6	7.2 ± 0.6	8.9 ± 1.1	7.8 ± 0.6	7.2 ± 0.6
Lidocaine	5.6 ± 0.6	7.2 ± 0.6	9.4 ± 1.1	7.2 ± 1.1	6.1 ± 0.6
Leukocytes, $10^3 \cdot mm^{-3}$					
Saline	7.0 ± 0.3	13.1 ± 0.7	12.5 ± 0.5	10.5 ± 1.0	10.1 ± 1.0
Lidocaine	7.1 ± 0.4	12.2 ± 0.7	11.6 ± 0.6	8.5 ± 0.6	8.7 ± 0.6
C-reactive protein, mg/l					
Saline	9 ± 3	7 ± 2	13 ± 3	63 ± 11	75 ± 13
Lidocaine	7 ± 3	6 ± 1	11 ± 2	59 ± 9	73 ± 9

+2 through +48 h refers to hours after surgery. Values of cortisol, epinephrine, norepinephrine, glucose, C-reactive protein, and leukocyte count refer to plasma concentrations and are given in SI units where appropriate. Data are presented as mean ± SEM. There were no statistically significant differences between the lidocaine and saline groups.

Preop = preoperative measurement.

a more profound blockade of nociception such as that achieved by epidural anesthesia.[8] But on the other hand—and more importantly—it demonstrates that major benefits in postoperative recovery can be obtained without blocking the surgical stress response.

Systemic lidocaine also improved postoperative bowel function. Defecation occurred almost 1 day earlier in the lidocaine group. In fact, the reduction of postoperative ileus duration is similar with intravenous lidocaine and novel (and expensive) quaternary opioid-receptor antagonists currently in phase III testing.[42–44] Postoperative ileus results from several factors, including postoperative opioid consumption, visceral inflammation secondary to surgery, and postoperative sympathetic stimulation.[11,12,45] The reduction in ileus duration by intravenous lidocaine may be mediated by the reduction of postoperative opioid consumption, the antiinflammatory properties of lidocaine, and/or a direct inhibition of the sympathetic myenteric plexus.

Our results complement findings reported by others including Groudine *et al.*[16] and Koppert *et al.*[17] The sparing effect of intravenous lidocaine on postoperative opioid consumption was confirmed. However, we in addition demonstrated that intravenous lidocaine improves pain scores more during activity than at rest, which is particularly important when patients are submitted to an acute rehabilitation program. Furthermore, visceral pain seemed to be sensitive to the analgesic action of lidocaine. Whereas most of the studies restricted the intravenous infusion of lidocaine to the intraoperative and the immediate postoperative (postanesthesia care unit) periods, the infusion was maintained for 24 h postoperatively in our study. Indeed, because some actions of lidocaine such as leukocyte inhibition are

clearly time dependent,[46] we decided to prolong this therapy during the postoperative period. Whether prolonging the lidocaine infusion improves analgesia cannot be ascertained by this study. As far as bowel function is concerned, comparison of the data in our case series using lidocaine intraoperatively only[22] and the results of the current study suggests that times to first flatus, defecation, and hospital discharge are all shortened when the intraoperative lidocaine infusion is prolonged postoperatively.

The various benefits of intravenous lidocaine integrated in an acute rehabilitation program allowed patients to leave the hospital 1 day earlier. In fact, the results of this prospective study confirm the findings of our case series,[22] compare favorably with the results of others[4,13] using epidural anesthesia, and suggest that the systemic actions of lidocaine rather than nerve block *per se* may play a major role in the beneficial effects on postoperative recovery observed with epidural analgesia. Hence, systemic local anesthetics might be a possible alternative in patients unable or unwilling to receive epidural therapy. These findings also suggest that patient-controlled analgesia with opiates may not be the appropriate control group in studies assessing benefits of epidural treatment, but that systemic local anesthetics should be used as a comparison instead.

Intravenous infusion of lidocaine reduced the amount of sevoflurane required to maintain hemodynamic stability and BIS during surgery. This reduction was observed despite a (modestly) decreased requirement for sufentanil. This result is in distinct contrast to three recent human studies in which lidocaine was not shown to reduce anesthetic requirements.[26–28] Plasma concentrations of lidocaine in these studies were similar to ours.

However, pain in those studies was induced with short tetanic electrical stimuli. Modulation of windup phenomena, hypersensitization, and inflammatory responses may all play roles in the effect of lidocaine on anesthetic requirement, and those events might require sustained noxious stimulation to develop.[47,48] Short electrical stimuli may thus poorly model actual surgical pain in this regard. The depth of anesthesia, as measured by BIS, was virtually identical in both groups. Similar intraoperative catecholamine levels in both groups also indicate that the sevoflurane reduction observed during lidocaine infusion did not result in inadequate anesthetic depth and that the effect of lidocaine on hemodynamic responses to surgery does not result from direct inhibition of the cardiovascular system.

The dose of lidocaine we used was in the established range for treatment or prophylaxis of ventricular arrhythmias.[20] Although a continuous infusion might lead to accumulation over time, the concentrations measured in this and other studies[16,17] remained well below toxic levels even after 24 h. Furthermore, concentrations remained similar or smaller than those reported during prolonged epidural administration of lidocaine.[49,50] However, this study was not powered to assess safety of the approach, and a larger-scale trial will be needed to determine whether occasional patients may develop toxicity in this setting.

In summary, we demonstrated that perioperative administration of low doses of intravenous lidocaine reduces intraoperative anesthetic requirements and has a clinically relevant beneficial effect on postoperative recovery after colectomy. These data suggest that intravenous local anesthetics can contribute to postoperative acute rehabilitation programs.

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