Intravenous Lidocaine Is as Effective as Epidural Bupivacaine in Reducing Ileus Duration, Hospital Stay, and Pain After Open Colon Resection

A Randomized Clinical Trial

Brian R. Swenson, MD, MS, Antje Gottschalk, MD,† Lynda T. Wells, MBBS,† John C. Rowlingson, MD,† Peter W. Thompson, MS,‡ Margaret Barclay, ACNP,* Robert G. Sawyer, MD,*§ Charles M. Friel, MD,* Eugene Foley, MD, FASCRS,* and Marcel E. Durieux, MD, PhD†*

Background: Both postoperative epidural analgesia and intravenous (IV) infusion of local anesthetic have been shown to shorten ileus duration and hospital stay after colon surgery when compared with the use of systemic narcotics alone. However, they have not been compared directly with each other.

Methods: Prospective, randomized clinical trial was conducted comparing the 2 treatments in open colon surgery patients. Before induction of general anesthesia, patients were randomized either to epidural analgesia (bupivacaine 0.125% and hydromorphone 6 μg/mL were started at 10 mL/hr within 1 hr of the end of surgery) or IV lidocaine (1 mg/min in patients <70 kg, 2 mg/min in patients ≥70 kg). Markers of return of bowel function, length of stay, postoperative pain scores, systemic analgesic requirements, and adverse events were recorded and compared between the 2 groups in an intent-to-treat analysis.

Results: Study enrollment took place from April 2005 to July 2006. Twenty-two patients were randomized to IV lidocaine therapy and 20 patients to epidural therapy. No statistically significant differences were found between groups in time to return of bowel function or hospital length of stay. The median pain score difference was not statistically significant. No statistically significant differences were found in pain scores for any specific postoperative day or in analgesic consumption.

Conclusions: No differences were observed between groups in terms of return of bowel function, duration of hospital stay, and postoperative pain control, suggesting that IV infusion of local anesthetic may be an effective alternative to epidural therapy in patients in whom epidural anesthesia is contraindicated or not desired.

(*Reg Anesth Pain Med* 2010;35: 370–376)

Postoperative ileus has profound detrimental effects on recovery after abdominal surgery. Lack of enteral nutrition delays wound healing and discharge and increases morbidity. Postoperative epidural local anesthetic infusion is the most effective approach to shorten the duration of postoperative ileus.[1] Its mechanism of action, however, is unclear. Because postoperative ileus is in part inflammatory in origin,[2] it has been suggested that the beneficial effects of epidural local anesthetics on bowel function may result from the anti-inflammatory action of the local anesthetic.[3] Local anesthetics modulate the inflammatory system,[4,5] and because epidural anesthesia leads to significant, sustained blood levels of local anesthetic,[4] it is conceivable that these are responsible for the beneficial effects of epidural analgesia on duration of postoperative ileus.

Several randomized, placebo-controlled clinical trials have demonstrated that intravenous (IV) lidocaine administration similarly reduces the duration of postoperative ileus and accelerates hospital discharge[6,7] when compared with systemic narcotic analgesia. In addition, most of these studies reported decreased postoperative pain in patients receiving lidocaine. This less invasive approach to postoperative management would likely be simpler and potentially safer than epidural local anesthetic administration.

However, a direct comparison between IV and epidural local anesthetic has not been performed. In addition to comparing the effect on ileus, it is essential to ensure that postoperative pain is not worse in patients receiving IV lidocaine as compared with those receiving epidural local anesthetic. The present randomized trial was therefore designed to test the hypothesis that perioperative administration of IV or epidural local anesthetics in combination with epidural hydromorphone in patients undergoing open colon surgery would result in similar pain scores and ileus duration (primary end point).

METHODS

Participants

The trial was approved by the institutional review board of the University of Virginia, and written informed consent was obtained from all subjects. Patients aged 18 to 75 years of American Society of Anesthesiologists (ASA) physical status classes I, II, or III, scheduled for elective colon resection were eligible. Exclusion criteria included allergy to local anesthetics, myocardial infarction within 6 months before surgery, liver disease (aspartate aminotransferase, alanine aminotransferase, or bilirubin >2.5 times the upper limit of normal), renal impairment (creatinine clearance <60 mL/min), systemic corticosteroid use, chronic use of opiates, unwillingness or contraindication to epidural analgesia, pregnancy, or active breast-feeding.

Treatment

On the day of surgery, consenting patients were randomized to either an IV infusion of local anesthetic (lidocaine) or epidural analgesia (bupivacaine + hydromorphone). Patient assignments

From the Departments of *Surgery and †Anesthesiology, University of Virginia Health System; ‡School of Medicine, University of Virginia; and §Department of Health Evaluation Sciences, University of Virginia Health System, Charlottesville, VA.

Accepted for publication November 13, 2009.

Address correspondence to: Marcel E. Durieux, MD, PhD, Department of Anesthesiology, PO Box 800710, Charlottesville, VA 22908-0710 (e-mail: durieux@virginia.edu).

This clinical trial has been registered with the US National Institutes of Health, ClinicalTrials.gov identifier: NCT00600158.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e3181e8d5da

were generated using a published table of random numbers and stored in sealed envelopes before initiation of the study protocol.

Anesthetic management was standardized and based on the standard of care in our institution. General anesthesia was provided to all patients using propofol for induction (including a single bolus of lidocaine <1.5 mg/kg), followed by maintenance of anesthesia with a volatile inhaled anesthetic (isoflurane, sevoflurane, or desflurane) in 40% to 100% oxygen (no nitrous oxide). For intraoperative analgesia, patients could receive fentanyl and/or morphine. The choice of neuromuscular agent was left to the discretion of the anesthesia provider.

In the recovery area, pain was assessed using an 11-point verbal scale (0–10) every 15 mins, and scores greater than 3 were treated with either fentanyl 50 μg every 10 mins or morphine 4 mg every 20 mins as needed.

After transfer to the ward, all patients received patient-controlled analgesia for breakthrough pain. Initial patient-controlled analgesia setting included morphine 2 mg IV demand dose with 6-min lockout interval (10 mg/hr maximum). Fentanyl was used in an appropriate dose if the patient reported an allergy to morphine. Pain scores were monitored as well from the Acute Pain Service as from the floor nurse and recorded every 4 hrs while patients were awake.

All intraoperatively placed nasogastric tubes were removed immediately before extubation. On the day of surgery and on the first postoperative day, patients did not take anything by mouth. Diet advancement was guided by return of bowel function.

Patients were mobilized on day of surgery. They ambulated twice on the first postoperative day and 3 times on the second postoperative day and walked alone beginning on the fourth postoperative day.

All patients were instructed to report the time of first flatus and bowel movements; the patient informed the nursing staff, who documented the time. The day after this first sign of return of bowel function, the study intervention was discontinued. If therapy outside the standard protocol was required, the patient was withdrawn from the study and followed in an intent-to-treat manner for assessment of primary outcomes.

Patients were discharged at home after tolerating a solid diet and stating of bowel function, optimized pain control on oral pain medication and be able to perform or have help with their activities of daily living.

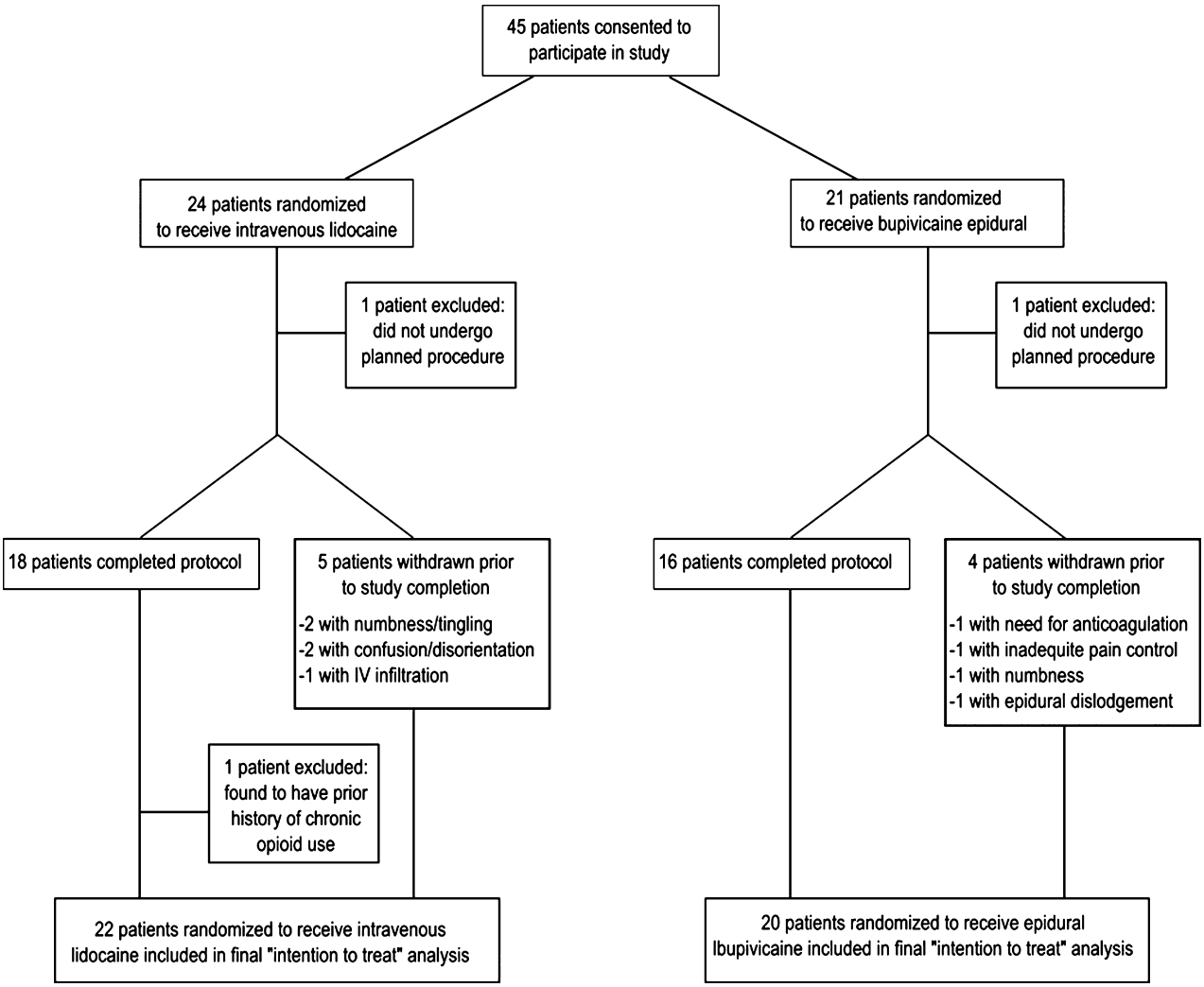

FIGURE 1. Randomization diagram.

IV Local Anesthetic

Patients randomized to the IV local anesthetic group received an IV infusion of lidocaine starting after anesthesia induction. We initially administered 2 mg/min in patients less than 70 kg and 3 mg/min in patients 70 kg or greater, as reported in the literature.[6] However, several patients reached potentially toxic plasma levels, and therefore, we reduced the dose in the remaining 11 patients to 1 mg/min in patients less than 70 kg and 2 mg/min in patients 70 kg or greater. Subgroup analysis showed no difference in the primary end point between the 2 dosing schemes, and we therefore pooled the data from the groups for further analysis.

The day after return of bowel function, the lidocaine infusion was turned off. If flatus had not occurred on the fifth postoperative day, IV lidocaine was discontinued.

Plasma lidocaine concentrations were determined in the recovery area and daily during treatment with IV lidocaine. The infusion was suspended at the first sign of any adverse event, and an additional plasma lidocaine concentration was measured. In case of lidocaine levels greater than 5 μg/mL without any adverse signs or symptoms, the lidocaine infusion rate was decreased by half.

Epidural Analgesia

Before induction of general anesthesia, patients randomized to the epidural local anesthetic group had an epidural catheter placed between the 8th through 12th thoracic vertebrae. Bupivacaine 0.125% and hydromorphone 6 μg/mL were started at 10 mL/hr within 1 hr of the end of surgery. A dedicated hospital anesthesia epidural team evaluated the patients after emergence from anesthesia in the postanesthesia care unit. At this time, the epidural catheter was dosed at the discretion of this team. This included additional boluses of the original mixtures, along with changes in the rate of infusion.

The day after the first sign of return of bowel function, the epidural team removed the epidural catheter. If flatus has not occurred on the fifth postoperative day, the epidural catheter and the epidural infusion could be continued at the discretion of the epidural team and surgeon.

Statistical Analysis

Before patient enrollment, a power analysis was performed based on findings by Groudine et al.[6] In this study, patients from the control group had their first bowel movement after 73.9 ± 16.3 hrs; a 20% reduction in our primary end point of time to return of bowel function (differences in the mean of 15 hrs) was considered clinically significant. A comparison between the 2 groups using a 2-tailed t test for independent samples with an α of 0.05 and $1 - \beta$ of 0.8 would require 19 patients per group. We anticipated a few study withdrawals (3–4 subjects/subgroup) and therefore enrolled 45 subjects total.

Primary outcomes were analyzed using an intent-to-treat analysis. Categorical variables were compared using χ^2 analysis and Fisher exact test. Continuous variables were compared using the Mann-Whitney U rank sum test. Pain scores and opiate consumption were averaged for each patient for each postoperative day as well as in a 5-day average. When fentanyl was used rather than morphine, it was converted to morphine equivalents using a conversion ratio of 100 μg fentanyl = 10 mg morphine. Median pain scores and analgesic usage were then compared between groups. Additionally, pain was compared using the area under a hypothetical pain/time plot to attenuate recording bias. Data analysis was performed using SAS version 9.1.3 (SAS Institute, Cary, NC) and Sigma Plot 10.0 (Systat Software, Inc, San Jose, Calif).

RESULTS

Study enrollment took place from April 2005 to July 2006. During this time, 45 patients consented to participate, 21 were initially randomized to epidural therapy and 24 to IV lidocaine therapy. In the IV lidocaine group, 11 received the reduced dosage of 1 mg/min.

A diagram outlining the randomization and subsequent treatment of the 2 groups is presented in Figure 1.

Baseline demographic and perioperative information for the 2 groups is provided in Tables 1–3. The groups were similar in terms of age, body mass index, presenting diagnosis, and operative time. There were differences in the proportion of female patients (20% in the epidural group and 55% in the IV lidocaine group; $P = 0.021$) and distribution of ASA scores ($P = 0.014$: the IV lidocaine arm included all the ASA III patients). The total duration of epidural infusion was 91 hrs 36 mins (±41 hrs 3 mins); in the IV lidocaine group, the duration of the lidocaine infusion was 69 hrs and 54 mins (±28 hrs 14 mins).

TABLE 1. Baseline Demographic and Perioperative Characteristics of Patients

	Epidural (n = 20)	IV Lidocaine (n = 22)	*P*
Age, y	49 (36–54)*	52 (40–62)	0.23
Female sex	4 (20%)	12 (55%)	0.021
BMI, kg/m^2	28 (22–31)	25 (19–29)	0.20
Presenting diagnosis			0.32
Malignancy	7 (35%)†	10 (46%)	
Inflammatory bowel disease	8 (40%)	7 (32%)	
Fistula	0 (0%)	1 (5%)	
Diverticulitis	3 (15%)	0 (0%)	
Prolapse	0 (0%)	2 (9%)	
Other	2 (10.0%)	2 (9%)	
ASA score			0.014
I	1 (5%)	1 (5%)	
II	18 (95%)	14 (64%)	
III	0 (0%)	7 (32%)	
Procedure performed			0.0066
Subtotal colectomy	4 (20%)	2 (9%)	
Total abdominal colectomy	1 (5%)	0 (0%)	
LAR/APR/IPAA	12 (60%)	20 (91%)	
Lyses of adhesions, small-bowel resection with primary anastomosis and ileostomy	1 (5%)	0 (0%)	
Closure of end ileostomy with bowel resection	1 (5%)	0 (0%)	
Duration of surgery, min	175 (121–215)	181(112–222)	0.75

*Continuous variables are reported as median (interquartile range).

†Categorical variables are reported as n (%).

BMI indicates body mass index; LAR, low anterior resection; APR, abdominal-perineal resection; IPAA, ileal pouch–anal anastomosis.

TABLE 2. Intraoperative Medication

	IV Lidocaine Group	SD	Epidural Group	SD	*P*
Lidocaine for induction, average, mg	95 (n = 22)	28	87 (n = 14)	20	0.363
Propofol for induction, average, mg	170 (n = 22)	46	188 (n = 16)	50	0.268
Fentanyl intraoperatively, average, μg	418 (n = 21)	143	335 (n = 15)	159	0.112
Morphine intraoperatively, average, mg	10 (n = 16)	3.5	13 (n = 7)	6.5	0.156
Morphine equivalents during surgery, average	52 (n = 22)	17.2	33 (n = 18)	21.8	0.004
Maintenance with sevoflurane, n	9		11		0.409
Maintenance with desflurane, n	12		8		
Maintenance with isoflurane, n	1		0		
Relaxant vecuronium, average	11 (n = 16)	6.8	12 (n = 9)	5.6	0.881
Relaxant rocuronium, average	59 (n = 12)	23.8	63 (n = 12)	29.7	0.708
Fluids intraoperatively, average, mL	3763 (n = 22)	1817	4039 (n = 19)	1778	0.627

Data on time to return of bowel function and hospital length of stay were typical for our institution and are reported in Table 4. No differences between the 2 treatments were found between times to first flatus, first bowel movement, advancement to clear fluid, and tolerating 300-mL oral intake without nausea or vomiting. No significant differences were identified in inpatient time (time from end of procedure to time of discharge).

Pain scores were averaged over the 5 days of the study. The median pain scores were 2.2 (interquartile range, 1.6–3.4) in the epidural group and 3.1 (2.3–4.3) in the IV lidocaine group; this difference was not statistically significant ($P = 0.25$). A post hoc power analysis indicated that the study had 80% power to detect a difference of 1.3 in mean pain scores over 5 days. A second analysis of the area under a hypothetical pain/time plot revealed 1090 pain points-hours (551–2120 pain points-hours) in the epidural group and 1208 pain points-hours (753–1438 pain points-hours) in the IV lidocaine group; differences in these scores also were not statistically significant ($P = 0.91$). In a third analysis, we averaged patient pain scores for each postoperative day. Median pain scores for postoperative days 1 to 5 are reported graphically in Figure 2. Again, no statistically significant differences were found in pain scores for any specific postoperative day, although a trend was apparent for somewhat increased pain in the IV lidocaine group (approximately 1.5 points on a 10-point scale) immediately after surgery.

The similarity in pain scores could not be explained by a higher opiate use in the IV lidocaine group. We excluded 2 patients from this part of the analysis, both in the IV lidocaine group. Both had chronic pain and required opiate doses greater than 1500 mg morphine equivalents during their hospitalization (more than 10× the median for their group). One of them subsequently received an epidural catheter for further pain treatment. Although a trend was observed for somewhat greater opiate consumption in the IV lidocaine group (110 mg morphine equivalent [86–284 mg]) as compared with the epidural group (75 mg morphine equivalent [0–242 mg]), there were no significant differences in opiate consumption between the groups during the duration of hospitalization ($P = 0.115$). Data are presented as median (25%–75% interquartile range).

Similarly, there were no differences between the groups on each of the individual postoperative days. However, there was a suggestion that epidural local anesthetic might have been more effective than IV lidocaine early after surgery. For example, all patients in the IV lidocaine group used at least some opiate on the day of surgery and the first postoperative day, whereas 6 patients in the epidural therapy group did not require IV opiates on those days. However, patients in the epidural therapy group all received hydromorphone epidurally.

All patients experienced at least 1 adverse event, most of them mild. A summary of moderate or severe events is provided in Table 5. No statistically significant differences were found in either frequency or severity of adverse events in general, or for any specific event category.

Five adverse events in 3 patients were considered clinically significant by the treating physicians. On hospital day 3, 1 patient in the IV lidocaine group complained of strange sensations in the face, perioral numbness, shortness of breath, and a subjectively rapid heart rate. Lidocaine levels were less than the accepted

TABLE 3. Daily Opioid Consumption

Daily Morphine Consumption	Op. Day	POD 1	POD 2	POD 3	POD 4
Epidural group median, mg	25	57	40	29	30
25% Interval	11	27	7	12	18
75% Interval	50	100	74	89	87
Lidocaine group median, mg	17	48	23	20	7
25% Interval	8	30	17	14	4
75% Interval	56	83	76	64	59
P	0.884	0.961	0.883	0.657	0.111

Op. Day indicates operative day; POD, postoperative day.

TABLE 4. Time to Return of Bowel Function and Length of Stay*

Measures of Return of Bowel Function,† d	Epidural (n = 20)	IV Lidocaine (n = 22)	*P*
Time to first flatus	1.6 (1.2–34)†	2.7 (1.9–3.5)	0.17
Time to first bowel movement	3.0 (1.7–4.5)	2.9 (2.3–3.6)	0.99
Time of advancement to clear liquid diet‡	3.6 (2.6–4.8)	2.9 (2.7–3.7)	0.47
Inpatient time§	5.3 (4.7–7.9)	5.1 (4.8–5.9)	0.80

Values are reported as median (interquartile range).

*Integer value of length of stay, as used by hospital administration.

†All times measured from completion of operative procedure to event.

‡Defined as the time at which the patient completed a 300-mL solid intake without nausea or vomiting.

§Time of completion of operative procedure to discharge time.

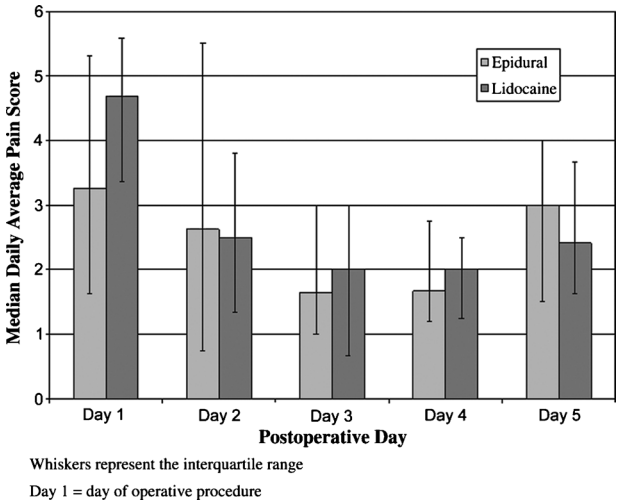

FIGURE 2. Median average daily pain scores by postoperative day. Whiskers represent the interquartile range. Day 1 = day of operative procedure.

toxic levels (<5 mg/mL) throughout the treatment period. Sensations were presumed to be anxiety related by the treating physicians, but IV lidocaine therapy was discontinued, and symptoms resolved. No further episodes occurred during hospitalization. One patient in the IV lidocaine group became disoriented and complained of visual hallucinations on hospital day 4. Lidocaine level at that time was 6.5 μg/mL (elevated). Study therapy was stopped. The patient's confusion gradually resolved by hospital day 6. The patient had been intermittently tachycardic throughout the admission, and on hospital day 7, the patient experienced an episode of ventricular tachycardia that required cardioversion and eventual placement of an implantable cardioverter defibrillator. One patient in the epidural group developed rapid atrial fibrillation on hospital day 2, which was resistant to pharmacological cardioversion. Epidural therapy was discontinued to begin systemic anticoagulation therapy.

One patient from the epidural group complained of abdominal distension, nausea, and vomiting on postoperative day 3, which were treated with nasogastric tube decompression.

DISCUSSION

We found IV lidocaine equally effective as epidural bupivacaine for both return of bowel function and postoperative pain control after open colorectal surgery. Analgesic consumption was similar between the groups, although trends suggest that with larger group sizes we might have observed a somewhat greater opioid usage in the IV lidocaine group.

Ileus seems an almost unavoidable adverse effect of most types of bowel surgery. The duration of postoperative ileus is frequently a major determinant of duration of hospitalization. Continuous local anesthetic epidural analgesia[2] is often used to minimize the duration of postoperative ileus. This effect seems specifically related to the use of local anesthetic, as postoperative epidural administration of opiates alone is without effect on ileus.[1]

The observation that nonsteroidal anti-inflammatory drugs are effective in reducing the duration of ileus suggests that inflammatory modulation can speed return of bowel function.[8] Similarly, the effectiveness of epidural local anesthetic may be due to anti-inflammatory effects. Modulating effects of local anesthetics on the inflammatory system are well known[4] and have been described in vitro,[5] in animal studies, and clinical trials.[6] The compounds have been shown to inhibit neutrophil priming (a critical component of neutrophil-mediated tissue injury[9]), but not to interfere with activation (required for wound healing and host defense).[4,10] Importantly, and in contrast to classic inflammatory suppression, this inflammatory modulation by local anesthetics is therefore not associated with detrimental effects on wound healing and infection rates. Because epidural anesthesia leads to low but consistent blood levels of local anesthetics (1–5 μM),[4] it is conceivable that the inflammatory modulatory action of systemically absorbed local anesthetic explains the beneficial effects of epidural analgesia on duration of postoperative ileus.

The analgesic and anti-inflammatory effect of systemic lidocaine, which persists after serum levels of lidocaine have decreased, may be a result of block or inhibition of nerve conduction.[6] This is related to the abilities of systemic lidocaine to depress spike activity, amplitude, and conduction time in both myelinated A-δ and unmyelinated C fibers significantly.[11] In addition, it has been shown that IV lidocaine decreased the heat-I capsaicin–induced secondary hyperalgesia via its central effect, which also suppressed secondary hyperalgesia in experimental incision-induced pain by inhibiting centralization.[12,13] Moreover, local anesthetics prevent hyperactivation of neutrophils, thereby preventing an overactive inflammatory response.[14]

TABLE 5. Adverse Events During the Study Period and In-Hospital Follow-Up

	Epidural	IV Lidocaine	
	n = 20	n = 22	*P*
Patients with 1 or more adverse events	20 (100)	22 (100)	—
Adverse events with moderate severity	12 (57)	16 (67)	0.53
Anemia	1 (5)	1 (5)	1.00
Anxiety	0 (0)	1 (5)	1.00
Supraventricular tachycardia	1 (5)	3 (14)	0.61
Back pain	1 (5)	0 (0)	0.48
Bradycardia	1 (5)	0 (0)	0.48
Confusion	0 (0)	2 (9)	0.49
Decreased oxygen saturation level	0 (0)	1 (5)	0.48
Dizziness/lightheadedness	1 (5)	1 (5)	1.00
Fever	1 (5)	1 (5)	1.00
Hyperglycemia	0 (0)	3 (14)	0.23
Hypertension	0 (0)	3 (14)	0.23
Itching	3 (15)	3 (14)	1.00
Lower-extremity numbness	6 (24)	1 (5)	0.10
Nausea	4 (20)	4 (18)	1.00
Intravascular device infection	1 (5)	0 (0)	0.48
Syncope	1 (5)	0 (0)	0.48
Vomiting	0 (0)	1 (5)	1.00
Wound infection	1 (5)	0 (0)	0.48
Adverse events with severe severity	1 (5)	3 (14)	0.61
Arrhythmia	1 (5)	1 (5)	1.00
Confusion	0 (0)	1 (5)	0.48
Facial numbness	0 (0)	1 (5)	0.48
Shortness of breath	0 (0)	1 (5)	0.48

Values are reported as n (%).

Several clinical trials indicate that systemic local anesthetics indeed have beneficial actions on the return of bowel function after surgery. In patients undergoing radical prostatectomy, administration of lidocaine (2 mg/min in patients <70 kg and 3 mg/min in patients ≥70 kg) for the duration of surgery and 1 hr postoperatively resulted in a 1-day earlier return of bowel function and an associated earlier discharge from the hospital as compared with placebo. A trial in patients undergoing laparoscopic colectomy showed similar benefits.[7] Significantly earlier return of propulsive motility in the colon was also observed in patients undergoing cholecystectomy who received IV lidocaine (3 mg/min intraoperatively and continued 24 hrs after surgery).[11] Similarly, intraoperative instillation of bupivacaine demonstrated beneficial effects on colonic motility.[15]

Epidural local anesthetic administration is also the criterion standard for postoperative pain control, and it is unclear if systemic local anesthetics would provide similarly effective analgesia. Brief infusions of lidocaine (intraoperatively and for 2 hrs postoperatively) reduced total pain scores during hospitalization from 13.25 to 4.67 after prostatectomy.[6] After laparoscopic colectomy, early postoperative opiate use was reduced by approximately 50% if IV lidocaine was administered during the procedure.[7] In agreement with these findings, we found pain scores to be comparable between the 2 arms of the study. A small, nonsignificant difference in favor of epidural therapy was observed on the day of surgery, but otherwise, pain scores were almost identical. This is remarkable because the epidural therapy group did receive epidural opioids in addition to local anesthetics.

Herroeder et al[16] compared a placebo group with an intervention group (systemic lidocaine infusion: bolus (1.5 mg) followed by a continuous infusion (2 mg/min) until 4 hrs postoperatively in patients undergoing colorectal surgery, and demonstrated that perioperative IV administration of lidocaine is associated with a shortened hospital stay. However, they failed to show differences in pain scores and opioid consumption. Kuo et al[17] compared thoracic epidural analgesia to IV lidocaine in their effects on cytokines, pain, and return of bowel function after colon surgery. They observed first flatus after 50.2 (±4.9) hrs in the thoracic epidural analgesia group and after 60.2 (±5.8) hrs in the IV lidocaine group. These results are consistent with those of the present study.

The use of IV local anesthetic to treat ileus and to assist in pain control has several advantages over epidural administration. The common use of perioperative anticoagulation for the prevention of deep venous thrombosis has made appropriate timing of epidural placement and removal considerably more difficult. Patients may not desire the placement of an epidural catheter. In addition, the uncommon but real risks of epidural placement would be avoided by systemic administration of the local anesthetic. However, there are also some potential problems associated with the use of systemic local anesthetics, including the risks of central nervous system and cardiac toxicity at higher doses. No differences were observed between groups in the number or severity of adverse events, and although causality cannot be determined, it is unlikely that the 3 clinically significant adverse events were related to study treatment in either arm.

Of particular importance is the potential effect on wound healing, as inflammatory modulation could potentially affect bacterial clearance. We observed no wound infections in the IV therapy group, as compared with a 25% infection rate in the epidural therapy group, but the study was not designed to assess this statistically. However, previous studies have shown no detrimental effects of IV local anesthetics on wound healing, and preclinical mechanistic studies indicate normal neutrophil function even in the presence of high concentrations of local anesthetics. Of course, if local anesthetics affect wound healing, one would expect this to occur independent of route of administration—IV or epidural.

In several patients, prolonged systemic lidocaine infusion resulted in plasma levels that exceeded 5 μg/mL. Although this was not associated with clinical toxicity, we did reduce the dosages used in the study, without any obvious effect on efficacy. Accumulation seemed to develop over days. We chose to administer IV lidocaine until bowel function returned, to mimic as closely as possible the procedure followed for epidural administration. However, previous studies have shown a significant benefit of IV lidocaine on return of bowel function and pain after infusions extending only 24 hrs[7] or even 1 hr[6] into the postoperative period, suggesting that the major portion of the local anesthetic benefit may be obtained during the intraoperative administration.

It should be realized that this study did not investigate the use of either epidural therapy or IV lidocaine as part of an accelerated recovery (fast-track) program. Whether IV lidocaine is equally effective as the proposed benefit of epidural analgesia when combined with other aggressive multimodal therapy cannot be deducted from our findings.

The present study has several limitations. First, the study was not blinded, and this may have influenced our results. However, we considered that blinding of an epidural infusion would be very difficult, if not impossible, and that therefore true blinding would be unlikely to be maintained even if attempted. If any placebo effect influenced our result, it would have been expected to be in favor of the more interventional approach, that is, epidural therapy. Second, we used 2 different local anesthetics: bupivacaine for epidural administration and lidocaine for IV administration. The reasons for this choice were to mimic as closely as possible the clinical setting. Bupivacaine is a standard drug for epidural therapy, and lidocaine would not be suitable in that setting as it is associated with more pronounced motor blockade. Conversely, bupivacaine is not suitable for IV administration because of concerns for cardiac toxicity. Because considerable data support the effectiveness of IV administration of lidocaine, and because in previous laboratory investigations we found very similar effects of bupivacaine and lidocaine on neutrophil function,[18] we chose to use different drugs for the 2 administration modes.

In conclusion, this trial indicates that IV lidocaine is as effective as epidural bupivacaine in accelerating the return of bowel function after colon surgery. In addition, the analgesic effects were similar. This suggests that systemic lidocaine may be an appropriate alternative to epidural therapy, particularly in the setting when epidural placement is technically difficult, contraindicated, or undesired. Investigation of the efficacy of shorter-term lidocaine infusions should be undertaken to assess whether these benefits can be achieved with even simpler protocols.

ACKNOWLEDGMENTS

The authors thank Marcia Birk, RN, for expert clinical coordination assistance; Justin Ford, MD, for assistance in data analysis; and James Click, BS, Maithili V. Chitnavis, and James Heckman, BS, for assistance with data collection.

REFERENCES

1. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev.* 2000:CD001893.

2. Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg*. 2000;87:1480–1493.
3. Hollmann MW, Strumper D, Durieux ME. The poor man's epidural: systemic local anesthetics for improving postoperative outcomes. *Med Hypotheses*. 2004;63:386–389.
4. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology.* 2000;93: 858–875.
5. Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. *Anesthesiology.* 2001;95:113–122.
6. Groudine SB, Fisher HA, Kaufman RP Jr, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg*. 1998;86:235–239.
7. Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology.* 2007;106:11–18.
8. Cheng G, Cassissi C, Drexler PG, Vogel SB, Sninsky CA, Hocking MP. Salsalate, morphine, and postoperative ileus. *Am J Surg*. 1996;171: 85–88; discussion 88–89.
9. Condliffe AM, Kitchen E, Chilvers ER. Neutrophil priming: pathophysiological consequences and underlying mechanisms. *Clin Sci (Lond)*. 1998;94:461–471.
10. Fischer LG, Bremer M, Coleman EJ, et al. Local anesthetics attenuate lysophosphatidic acid–induced priming in human neutrophils. *Anesth Analg*. 2001;92:1041–1047.
11. Rimback G, Cassuto J, Tollesson PO. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. *Anesth Analg*. 1990;70:414–419.
12. Dirks J, Fabricius P, Petersen KL, Rowbotham MC, Dahl JB. The effect of systemic lidocaine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. *Anesth Analg*. 2000;91:967–972.
13. Kawamata M, Takahashi T, Kozuka Y, et al. Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. *Pain*. 2002;100:77–89.
14. Hollmann MW, Kurz K, Herroeder S, et al. The effects of S(−)-, R(+)-, and racemic bupivacaine on lysophosphatidate-induced priming of human neutrophils. *Anesth Analg*. 2003;97:1053–1058.
15. Rimback G, Cassuto J, Faxen A, Hogstrom S, Wallin G, Tollesson PO. Effect of intra-abdominal bupivacaine instillation on postoperative colonic motility. *Gut*. 1986;27:170–175.
16. Herroeder S, Pecher S, Schonherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg*. 2007;246:192–200.
17. Kuo CP, Jao SW, Chen KM, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth*. 2006;97:640–646.
18. Hollmann MW, Herroeder S, Kurz KS, et al. Time-dependent inhibition of G protein–coupled receptor signaling by local anesthetics. *Anesthesiology.* 2004;100:852–860.