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Effects of Perioperative Analgesic Technique on Rate of Recovery after Colon Surgery

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Background: **Choice of perioperative analgesia may affect the rate of recovery of gastrointestinal function and thus duration and cost of hospitalization after colonic surgery.**

Methods: **Fifty-four patients undergoing partial colectomy surgery were randomized into four groups. All groups received a standardized general anesthetic. Group MB received a preoperative bolus of epidural bupivacaine and morphine followed by an infusion of morphine and bupivacaine. Group M received a preoperative bolus of epidural morphine followed by an infusion of morphine. Group B received a preoperative bolus of bupivacaine followed by an infusion of bupivacaine. Group P received a preoperative bolus of intravenous morphine followed by intravenous patient-controlled morphine postoperatively. All patients participated in a standardized recovery program to minimize the influence of nonanalgesic factors on recovery of gastrointestinal function. All epidural groups were double-blinded. All patients were deemed ready for discharge according to prospectively defined criteria.**

Results: **Groups B and MB reported superior analgesia with activity ($P < 0.01$). Group M had a greater incidence of pruritus ($P < 0.05$). Group B had a greater incidence of orthostatic hypotension ($P = 0.04$). Groups B and MB recovered gastrointestinal function and fulfilled discharge criteria approximately 1.5 days earlier than groups M and P ($P < 0.005$).**

Conclusions: **Epidural analgesia with bupivacaine and morphine provided the best balance of analgesia and side effects while accelerating postoperative recovery of gastrointestinal function and time to fulfillment of discharge criteria after colon surgery in relatively healthy patients within the context of a multimodal recovery program. (Key words: Analgesia: epidural. Anesthetics, local; bupivacaine. Anesthetics, opioids: morphine. Anesthetic techniques: epidural; patient-controlled analgesia. Gastrointestinal tract: gastrointestinal motility. Pain: postoperative; postoperative ileus.)**

THE current practice of medicine emphasizes that both quality and cost of medical care be constantly examined and improved. Postoperative ileus is a universal complication after major intraabdominal surgery that prolongs hospital stays and is estimated to have an annual cumulative United States healthcare cost of $750,000,000.[1] Previous studies suggest that multiple factors may affect the rate of postoperative recovery of gastrointestinal function after abdominal surgery. For example, recovery of postoperative gastrointestinal function may be promoted by early oral feeding,[2,3] use of low-fat oral nutrition,[4] early patient activity,[5] and administration of nonsteroidal anti-inflammatory agents.[6] In contrast, delayed recovery of gastrointestinal function has been associated with anastomotic surgery of the colon,[7] prolonged placement of nasogastric tubes,[8] and use of parenteral opioids.[9,10] The use of epidural analgesia, especially with local anesthetics, may accelerate the recovery of gastrointestinal function through blockade of inhibitory sympathetic re-

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flexes.[11–17] However, effects of epidural analgesia remain controversial, because previous studies have not controlled other factors that potentially affect the rate of recovery of gastrointestinal function. Thus, we designed a standardized postoperative recovery regimen to control and optimize factors known to affect rate of recovery of gastrointestinal function. Within this controlled setting, we performed a prospective, randomized, double-blinded study to examine the effects of different techniques of anesthesia and analgesia on recovery of gastrointestinal function and subsequent duration and cost of hospitalization.

Methods

A power analysis based on combined retrospective data from Virginia Mason Medical center and Mayo Clinic Jacksonville was performed. This analysis indicated that 12 patients per group would allow detection of difference in time until recovery of gastrointestinal function (flatus) of 2 days ($P = 0.05$, power = 0.8). After Institutional Review Board approval and obtaining participants' informed consent, 54 patients scheduled to undergo elective partial resection of the colon were enrolled in the study (41 from Virginia Mason and 13 from Mayo Clinic). Exclusion criteria included age younger than 35 or older than 80 yr, American Society of Anesthesiologists physical status IV or V, history of chronic pain or drug/alcohol dependence, history of allergy to local anesthetics or morphine, contraindications to ketorolac administration (serum creatinine clearance > 2 mg · dl^{-1}; history of hemorrhagic peptic ulcer disease; history of hypersensitivity to aspirin or other nonsteroidal anti-inflammatory agents), use of corticosteroids, presence of complete bowel obstruction, presence of inflammatory bowel disease, planned total colectomy or colostomy, previous history of abdominal radiation, and presence of infection or severe renal, hepatic, or cardiopulmonary disease.[18]

Protocol

All patients received standardized preoperative teaching, preoperative medication, and intraoperative general anesthesia (Appendix). On arrival at the preoperative holding area, each patient was randomized into one of four different perioperative analgesic groups: epidural morphine and bupivacaine (Group MB), epidural morphine (Group M), epidural bupivacaine (Group B), or intravenous patient-controlled (PCA) morphine (Group P). Separate randomization tables were prepared for each institution. The randomization was stratified by planned left *versus* right colonic anastomosis, because left colonic anastomosis may result in greater postoperative ileus.[7,19] An epidural catheter was inserted preoperatively in groups M, MB, and B at the T8–T10 vertebral interspaces and threaded 3 cm into the epidural space. After negative aspiration, medication was injected through the catheter before induction of general anesthesia according to the study group to which the patient was assigned:

Group MB (morphine + bupivacaine): 3 ml 0.75% bupivacaine containing epinephrine (15 μg) followed by an additional 7 ml 0.75% bupivacaine with epinephrine and 2 mg morphine. A continuous epidural infusion of plain bupivacaine 0.1% with morphine 0.03 mg · ml^{-1} was started within 30 min at a rate of 10 ml · h^{-1} and continued at this rate postoperatively.

Group M (morphine only): 3-ml test dose of lidocaine 1.5% containing epinephrine (15 μg) followed by 2-mg epidural dose of morphine. A continuous epidural infusion of morphine 0.05 mg · ml^{-1} was started within 30 min at a rate of 10 ml · h^{-1} and continued at this rate postoperatively.

Group B (bupivacaine only): 3 ml 0.75% bupivacaine containing epinephrine (15 μg) followed by an additional 7 ml 0.75% bupivacaine with epinephrine. A continuous epidural infusion of plain bupivacaine 0.15% was started within 30 min at a rate of 10 ml · h^{-1} and continued at this rate postoperatively.

Group P (Intravenous PCA) received 5 mg morphine intravenously after induction of general anesthesia.

Postoperative Analgesic Management

The epidural groups (MB, M, and B) were double blinded, and the epidural infusion was continued at a rate of 10 ml · h^{-1}. Analgesia at rest was titrated to a verbal pain score <5/10 (0 = no pain, 10 = worst possible pain) with an epidural injection of fentanyl 50 μg followed with an increase in the epidural infusion of 2 ml · h^{-1} every hour as needed. Because duration of epidural analgesia may affect rate of recovery of gastrointestinal function,[15] epidural analgesia was continued until patients satisfied discharge criteria. After study completion, epidural location of the catheter was assessed by injection of 5 ml 1% lidocaine.

Group P was unblinded due to ethical concerns over insertion of an epidural catheter for placebo purposes. Intravenous PCA morphine was begun in the postanes-

thesia care unit after an initial loading dose of up to 10 mg morphine. Initial PCA settings were dose of 1 mg with a lockout interval of 10 min. Analgesia at rest was titrated to a verbal pain score <5/10 with adjustments in PCA settings.

All patients received intramuscular ketorolac tromethamine 60 mg at the end of the operation. Intramuscular ketorolac 30 mg was continued every 6 h thereafter for a total of 72 h followed by ibuprofen 400 mg by mouth four times a day until discharge. For patients older than 65 yr, the doses of ketorolac were reduced by 50%. No other forms of analgesia or sedation were used.

Postoperative Management and Discharge Criteria

All patients were discharged from the postanesthesia care unit to the hospital floor and participated in a standardized recovery program. This program was designed to control factors that were previously identified as affecting recovery of gastrointestinal function.[20] Thus, the morning after surgery, nasogastric tubes were removed and patients were then fed a standardized low-fat, full liquid diet and ambulated. Before attempting ambulation, patients were assessed for evidence of motor blockade or orthostatic hypotension (>20% rise in heart rate or fall in blood pressure). If either was present, the epidural infusion was discontinued for 1 hr and then resumed at 75% of the original infusion rate, patients were again tested, and then ambulated. All patients receiving epidural analgesia had Foley catheters inserted for the duration of provision of epidural analgesia. Foley catheters were placed in the PCA patients at the discretion of the surgical team.

Patients were seen twice a day by surgical, anesthesia pain service, and research teams to optimize and coordinate care and to evaluate fulfillment of discharge criteria. Patients were deemed ready for discharge when oral nutrition could be tolerated without discomfort, gastrointestinal function had returned (defined as first passage of flatus), body temperature (tympanic membrane) was normal, and no major complications were present.

Collected Data

Preoperative and intraoperative data collection included patient demographic characteristics, duration of surgery, type of operation, type of surgical anastomosis (sewn *vs.* stapled), and intraoperative blood loss and fluid replacement. Postoperative data were collected 3 h after surgery, and every morning and evening until fulfillment of discharge criteria. Data were collected at Virginia Mason Medical Center by investigators and by research nurses at Mayo Clinic Jacksonville. Identical data collection tools were used at both institutions to maintain consistency. Measurements included visual analog pain scales (0 = no pain, 100 = worst imaginable pain) at rest, with ambulation, and with cough. Presence or absence of orthostatic hypotension (>20% rise in heart rate or fall in blood pressure), absolute hypotension (systolic blood pressure < 90 mmHg), nausea, pruritus, and sedation were noted by blinded observers. Total incidents of these side effects were divided by number of days of observation to calculate an average daily rate of incidence. Patients were instructed to record the time at which first passage of flatus was noted and were prompted to report this event at each visit. Daily intake of oral nutrition was noted. Suitability for discharge was assessed at each visit. An analgesia satisfaction questionnaire was completed by every study patient on discharge.

Data Analysis

Data were analyzed using contingency tables, factorial or repeated measures analysis of variance, or Kruskall Wallace test where appropriate. *Post hoc* testing was performed with Fisher's protected least significant test. A P value < 0.05 was considered significant.

Results

Fifty-four patients were enrolled into the study. Epidural catheters were unable to be placed in two patients who were withdrawn from protocol. After exclusion of these patients, 12 patients each in groups P and M and 14 patients each in groups MB and B remained for analysis.

Patient demographics, type of surgery and surgical anastomosis, duration of surgery, blood loss, and intraoperative fluid replacement were similar among all four groups (table 1).

Epidural groups MB and B reported lower pain scores with cough and ambulation ($P < 0.01$) than epidural group M or the PCA group (morning ambulation pain scores are displayed in fig. 1). Average daily consumption of analgesics are displayed in table 2. Side effects differed between groups: group B experienced a greater incidence of orthostatic hypotension and group M experienced a greater incidence of pruritus (table 3).

Two patients in group MB and one in group B required active warming (core temperature <32°C) during their stay in the postanesthesia care unit. All patients were equally satisfied with their analgesic management (table 2).

Groups MB and B recovered from postoperative ileus an average of 34 hr earlier (95% confidence interval for difference ranges from 22 to 46 h) than groups M and P (table 4). Indirect measurements such as daily oral intake and calorie counts were similar among groups (table 4).

Recovery of gastrointestinal function was the last discharge criterion to be met in all patients. Groups B and MB were ready for discharge an average of 35 h earlier (95% confidence interval for difference ranges from 27 to 49 h) than groups M and P (table 4). Actual time until discharge from hospital was greater than time until fulfillment of discharge criteria and was not different between groups (table 4).

Three patients, whose results were included in analysis, suffered adverse events. On further review, it was found that all three patients should have been excluded from participating in the study (1—presence of alcoholic cirrhosis, 2—chronic use of steroids for rheumatoid arthritis, and 3–history of congestive heart failure). The first two patients were randomized to the MB group and suffered anastomotic dehiscence requiring surgical reexploration. The third patient was randomized to the B group and developed congestive heart failure on the second postoperative day from an intracardiac shunt (due to occult atrial septal defect) leading to death. If these three patients had been correctly excluded at the outset, then time until actual hospital discharge would differ between groups (table 4). No other patients experienced adverse events or required hospital re-admission. There were no differences between operative surgeons (total of 12 from both institutions) in patient outcome.

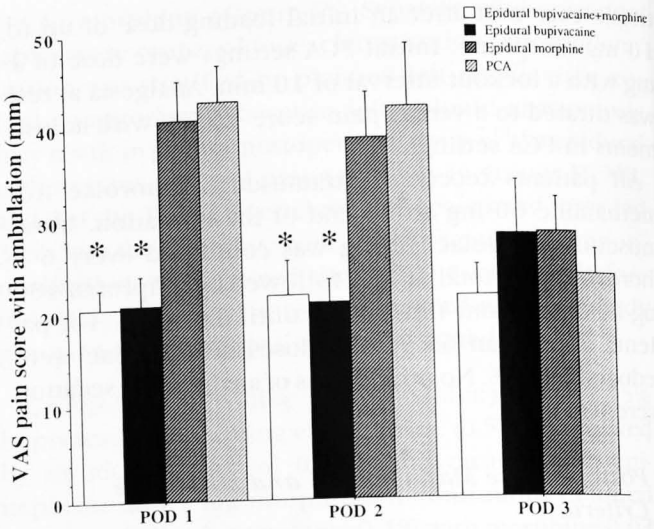

Fig. 1. Pain scores with morning ambulation. Mean and SE displayed. *Different from patient-controlled analgesia and epidural morphine groups ($P < 0.01$).

Table 1. Patient Demographic and Intraoperative Data

	Epidural Morphine Bupivacaine (Group MB)	Epidural Morphine (Group M)	Epidural Bupivacaine (Group B)	Intravenous PCA (Group P)
Age (yr)	62 ± 1	69 ± 1	63 ± 1	62 ± 1
Height (cm)	158 ± 1	151 ± 1	151 ± 1	147 ± 1
Weight (kg)	84 ± 2	71 ± 2	78 ± 2	76 ± 2
Sex (M/F)	8/6	7/7	7/5	5/7
Procedure (number)				
Right hemicolectomy	2	1	2	2
Left or transverse colectomy	12	13	10	10
Diagnosis (number)				
Cancer	10	9	9	9
Benign disease	4	5	3	3
Surgical Anastomosis (handsewn/staples)	7/7	6/8	6/6	7/5
Surgical duration (min)	212 ± 7	218 ± 8	220 ± 14	212 ± 9
Estimated blood loss (ml)	210 ± 17	175 ± 16	275 ± 26	275 ± 15
Intraoperative fluid replacement (ml)	3,305 ± 303	3,005 ± 95	3,545 ± 132	2,530 ± 169

PCA = patient-controlled analgesia.

Values are mean ± SE unless otherwise noted. There are no significant differences between groups according to contingency table and analysis of variance.

Table 2. Average Daily Analgesic Consumption and Patient Satisfaction with Postoperative Analgesia

	Epidural Morphine Bupivacaine (Group MB)	Epidural Morphine (Group M)	Epidural Bupivacaine (Group B)	Intravenous PCA (Group P)
Morphine ($mg \cdot h^{-1}$)	0.027 ± 0.002	0.052 ± 0.003		1.4 ± 0.2
Bupivacaine ($mg \cdot h^{-1}$)	9.0 ± 0.9		21.6 ± 1.5	
Overall quality of pain relief (1–10)	9.0 ± 0.1	9.3 ± 0.1	8.9 ± 0.1	8.9 ± 0.1
% that would choose this method of analgesia again	93	100	100	93

PCA = patient-controlled analgesia.
All values are mean ± SE unless otherwise noted.

Discussion

Our study demonstrates that technique of anesthesia and analgesia affects quality of analgesia, rate of recovery of gastrointestinal function, and time until fulfillment of discharge criteria. These differences may be explained by different mechanisms of action of the different analgesic techniques.

Analgesia and Side Effects

Administration of thoracic epidural bupivacaine and morphine (group MB) provided the best balance of analgesia *versus* side effects. The superior analgesia observed with activity may be explained by a combination of "preemptive analgesia,"[21,22] multimodal analgesia,[23] and analgesic synergism.[23,24]

Side-effect profiles varied for the different analgesic techniques. In agreement with previous studies, we noted a high incidence of orthostatic hypotension when analgesia was provided solely with epidural bupivacaine (group B)[25] and a high incidence of pruritus (44%) when analgesia was provided solely with epidural morphine (group M).[26] Combining epidural bupivacaine and morphine resulted in a lower incidence of side effects that may be due to synergistic interactions of epidural bupivacaine and morphine, which allowed the use of lower doses of each drug (table 2).[27] The low incidence of side effects in our study is similar to that previously reported in a study examining 4,227 postoperative patients receiving epidural bupivacaine and morphine for postoperative analgesia.[28] In addition, our use of thoracic, rather than lumbar, epidural catheters may also have contributed to a low incidence of side effects.[29,††] Thus, our results agree with those of previous studies and suggest that a combination of thoracic epidural bupivacaine and morphine provides excellent analgesia with a relatively low incidence of side effects.

Recovery of Gastrointestinal Function

Postoperative ileus appears to be most severely prolonged in the colon,[30–33] and operations involving colonic anastomoses result in especially severe ileus.[7] Thus, it is not surprising that recovery of gastrointestinal function was the last discharge criterion to be met in our patients. The most common theory for the cause of postoperative ileus is that abdominal pain activates a spinal reflex arc, which inhibits intestinal motility.[34] Furthermore, perioperative surgical stress induces generalized sympathetic hyperactivity, which further inhibits organized bowel motility.[1,35] Epidural administration of local anesthetics may improve bowel motility through blockade of both proposed mechanisms of ileus. Blockade of nociceptive traffic can disrupt the afferent limb of the spinal reflex arc. Furthermore, epidural local anesthetics can block both the efferent limb of this spinal reflex and the stress-related inhibitory output of thoracolumbar sympathetic efferents.[36–38] In addition, blood flow to the bowel is a critical factor for gastrointestinal motility,[39] and some authors have suggested that increased colonic blood flow resulting from the sympathetic blockade[40] may also contribute to reduction of ileus.[39] Thus, the accelerated rate of recovery in the groups receiving epidural local anesthetics (groups B and MB) may be due to local anesthetic blockade of afferent nociceptive information and/or sympathetic efferent activity.

In contrast to local anesthetics, epidural and systemic opioids do not block transmission in somatic or sympathetic nerves[41] and may directly inhibit gastrointes-

†† Wild LR: Does continuous infusion of epidural bupivacaine for postoperative pain impair functional mobility? (Abstract) 7th World Congress on Pain, August 22–27, 1993, Paris, France.

Table 3. Average Daily Incidence of Side Effects (%)

	Epidural Morphine Bupivacaine (Group MB)	Epidural Morphine (Group M)	Epidural Bupivacaine (Group B)	Intravenous PCA (Group P)
Pruritus	21	58*	14	125
Nausea	14	17	14	8
Orthostatic hypotension (>20% change in heart rate or blood pressure with change from supine to sitting)	14	17	57*	17
Absolute hypotension (systolic blood pressure <90 mmHg)	14	17	36	8

PCA = patient-controlled analgesia.

* Different from all other groups ($P < 0.05$) as determined with Fisher's exact test.

tinal motility.[9,42] Some studies have suggested that epidural opioids may be advantageous during recovery from ileus,[10] however our results indicate that epidural administration of morphine alone (group M) was no different than intravenous PCA morphine, and recovery in both groups was delayed as compared to the epidural local anesthetic groups.

Although previous studies have attempted to determine effects of analgesia on recovery of gastrointestinal function,[11–17] none of these studies have controlled for nonanalgesic factors that may also influence rate of recovery. Thus, we specifically designed a standardized postoperative recovery program to optimize recovery of gastrointestinal function.[20] All patients received preoperative education,[43] had nasogastric tubes removed the morning after surgery,[8] were fed a low-fat, liquid diet the morning after surgery,[2] were ambulated the day after surgery,[5] and received nonsteroidal anti-inflammatory agents (ketorolac and ibuprofen).[6,44] The use of nonsteroidal anti-inflammatory agents, in particular, has been demonstrated to reduce ileus in experimental models[45] and clinical studies.[6,44] The ability of nonsteroidal anti-inflammatory agents to reduce ileus may be due to reduction of inhibitory prostaglandins,[45] reduction of the surgical stress response,[46] and reduction of opioid consumption.[47] Thus, control of these factors likely reduced variability and aided our ability to study the effects of the different analgesic regimens on recovery of gastrointestinal function.

Two of our subjects had anastomotic dehiscence, and the incidence of this complication in our study (3.8%) compares favorably with that of previous studies that report a range of 7–13%.[12,17,48–50] Both of these subjects were enrolled in Group MB, and some investigators have proposed that use of epidural local anesthetics can lead to excessive colonic propulsive activity causing dehiscence of surgical anastomoses.[12,51] However, this concern is based on a few case reports,[12,51] is inconsistent with animal studies that demonstrate excellent healing of anastomoses,[52] and is refuted by clinical studies that actually demonstrate a modest trend toward a lower incidence of dehiscence with epidural analgesia.[17,48] Finally, we note that both of these patients were enrolled in violation of our exclusion criteria

Table 4. Recovery of Gastrointestinal Function and Time Until Hospital Discharge

	Epidural Morphine Bupivacaine (Group MB)	Epidural Morphine (Group M)	Epidural Bupivacaine (Group B)	Intravenous PCA (Group P)
Time until first flatus (h)	43 ± 4*	71 ± 4	40 ± 2*	81 ± 3
Calories consumed on day of discharge ($kcal \cdot kg^{-1}$)	19 ± 1	18 ± 1	20 ± 1	21 ± 2
Oral intake on day of discharge ($ml \cdot kg^{-1}$)	32 ± 2	35 ± 3	36 ± 2	35 ± 2
Time until fulfillment of discharge criteria	67 ± 8*	102 ± 13	62 ± 5*	96 ± 7
Time until actual hospital discharge	199 ± 71 (96 ± 12†)	130 ± 14	101 ± 11	122 ± 9

PCA = patient-controled analgesia.

Values are mean ± SE.

* Different from groups M and PCA ($P < 0.005$) as determined with analysis of variance followed by Fisher's protected least signficant difference.

† Value after exclusion of incorrectly enrolled subjects. After exclusion groups M and MB are different from groups M and PCA ($P < 0.04$).

(regular use of systemic corticosteroids and alcoholic cirrhosis), and thus underlying medical problems likely placed these patients at increased risk of adverse outcomes.[18] Nonetheless, an association between use of epidural analgesia and an increased risk of postoperative anastomotic dehiscence cannot be excluded. We stress that this protocol was intended only for relatively healthy patients, and additional studies should be performed before our results are extrapolated to less healthy populations.

Fulfillment of Discharge Criteria and Actual Hospital Discharge

Duration of postoperative hospitalization is multifactorial, and a single intervention that is not coordinated with other recovery factors may have little impact. This may explain why previous studies examining effects of epidural analgesia on duration of hospitalization have yielded inconsistent findings.[11–16] In contrast, we optimized and standardized multiple aspects of postoperative recovery and prospectively defined discharge criteria. After control of these factors, our results indicate that use of epidural analgesia with morphine and bupivacaine (group MB) shortens time until fulfillment of discharge criteria after elective colon surgery while providing the best balance of analgesia and side effects. Based on average charges at our institution, the use of epidural morphine and bupivacaine potentially generates a net savings of $1,200 per patient as compared with the use of epidural or PCA morphine.

Despite prospective agreement with all surgeons and education of patients, nurses, and residents, some patients were not discharged on fulfillment of discharge criteria. Various factors prevented timely hospital discharge including travel arrangements, social situations, and patient or surgeon desire for continued hospital-based observation. Nonetheless, our study used prospectively defined discharge criteria that were acceptable to a broad group of clinicians and identifies the potential for accelerated postoperative recovery via selection of analgesic technique.

Several aspects of study design deserve comment. First, the lack of double blinding of the PCA group is a potential source of bias. The prevailing impression among medical staff at both institutions was that epidural analgesia improved patient outcome. Thus, generalized care giver and observer bias may have affected measurements from the PCA group. Second, our use of a standardized, multimodal recovery program to accelerate postoperative recovery could be potentially criticized. However, this program allowed us to examine the effects of perioperative analgesia on rate of recovery after optimization and control of multiple recovery parameters, and our results indicate that choice of analgesia can still have an impact within the context of our recovery program. Further support for the use of a multimodal recovery program can be found in the observation that duration of hospitalization of our patients was shorter than previously reported after similar surgery.[50,53] Indeed, the recently published practice guidelines for acute pain management in the perioperative setting by the American Society of Anesthesiologists recommends the involvement of anesthesiologists in the formation of such recovery programs.[54] Finally, we intended to enroll only relatively healthy patients undergoing a single type of surgical procedure expected to result in severe postoperative ileus.[7] Thus, with the exception of the three patients enrolled in violation of exclusion criteria, our patients readily tolerated their accelerated convalescence, and recovery of gastrointestinal function was the rate-limiting factor to fulfillment of discharge criteria. Although our results should be applicable to other abdominal procedures and patient populations, we stress that additional studies should be performed before generalized use of this protocol. Nonetheless, our small clinical trial suggests that choice of perioperative analgesic technique can affect duration and cost of hospitalization in healthy patients when combined with a multifactorial recovery program.

In summary, epidural analgesia with bupivacaine and morphine provided the best balance of analgesia and side effects while accelerating postoperative recovery of gastrointestinal function and time to fulfillment of discharge criteria in relatively healthy patients within the context of a multimodal recovery program.

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Appendix

Preoperative Teaching

Patients were informed that nasogastric tubes would be removed the morning after surgery, that they would ambulate the morning after surgery, that they could eat a low-fat, full liquid diet the morning after surgery, that pain control would be excellent, and that expected length of hospital stay would be 4–6 days.

Preoperative Medication

On arrival at the preoperative holding area, all patients received intravenous sedation consisting of midazolam 0.02–0.04 $mg \cdot kg^{-1}$ and fentanyl 0.75–1.5 $\mu g \cdot kg^{-1}$.

Intraoperative Anesthetic

General anesthesia was induced in all study groups with intravenous fentanyl 2 $\mu g \cdot kg^{-1}$, thiopental 2–5 $mg \cdot kg^{-1}$, and succinylcholine 1.5 $mg \cdot kg^{-1}$ (after pretreatment with 3 mg of curare). Anesthesia was maintained with oxygen and isoflurane (to a maximum of 2% end-tidal concentration) as needed to treat evidence of inadequate anesthesia and to maintain hemodynamic stability (blood pressure and heart rate ± 20% of preoperative baseline). Neuromuscular relaxation was provided with pancuronium in doses determined by neuromuscular monitoring, and then reversed with intravenous neostigmine 0.05 $mg \cdot kg^{-1}$ and intravenous glycopyrrolate 0.01 $mg \cdot kg^{-1}$ at the conclusion of the operation. Maintenance intraoperative fluid was provided at a rate of 8 $ml \cdot kg^{-1} \cdot h^{-1}$ with balanced salt solution. Intraoperative blood loss was replaced with crystalloid in a 3:1 ratio. Blood pressure and heart rate were maintained at ±30% of baseline. Hypotension (mean blood pressure >30% below baseline) was treated with a 500-ml bolus of balanced salt solution and/or 5–10 mg intravenous doses of ephedrine followed by an increase in maintenance fluids to a rate of 10 ml/h. If hypotension persisted after administration of 1,000 ml saline and >25 mg ephedrine, a phenylephrine and/or dopamine infusion was begun. Bradycardia (heart rate >30% below baseline or <50 beats/min) was treated with atropine 0.2 mg intravenous every 1–3 min to a maximum of 1 mg. Hypertension/tachycardia (mean blood pressure/heart rate >30% above baseline) was treated with an increase in isoflurane up to a 2% end-tidal concentration. If hypertension/tachycardia persisted, epidural groups received an epidural bolus of 50 μg of fentanyl mixed with 10 ml of the solution used for the continuous epidural infusion (11 ml total bolus volume), whereas the PCA group received 50 μg intravenous fentanyl every 2–3 min up to 2 $\mu g \cdot kg^{-1}$. If these treatments were not effective, esmolol or labetalol was administered.