Anesthesiology 2001; 95:1054–67

Double-masked Randomized Trial Comparing Alternate Combinations of Intraoperative Anesthesia and Postoperative Analgesia in Abdominal Aortic Surgery

Edward J. Norris, M.D., M.B.A., Charles Beattie, M.D., Ph.D.,† Bruce A. Perler, M.D.‡ Elizabeth A. Martinez, M.D.,§ Curtis L. Meinert, Ph.D.,‖ Gerald F. Anderson, Ph.D.,# Jeffrey A. Grass, M.D.,** Neil T. Sakima, M.D.,§ Randolph Gorman, M.D.,†† Stephen C. Achuff, M.D.,‡‡ Barbara K. Martin, Ph.D.,§§ Stanley L. Minken, M.D.,‖‖ G. Melville Williams, M.D.,‡ Richard J. Traystman, Ph.D.##*

Background: **Improvement in patient outcome and reduced use of medical resources may result from using epidural anesthesia and analgesia as compared with general anesthesia and intravenous opioids, although the relative importance of intraoperative *versus* postoperative technique has not been studied. This prospective, double-masked, randomized clinical trial was designed to compare alternate combinations of intraoperative anesthesia and postoperative analgesia with respect to postoperative outcomes in patients undergoing surgery of the abdominal aorta.**

Methods: **One hundred sixty-eight patients undergoing surgery of the abdominal aorta were randomly assigned to receive either thoracic epidural anesthesia combined with a light general anesthesia or general anesthesia alone intraoperatively and either intravenous or epidural patient-controlled analgesia postoperatively (four treatment groups). Patient-controlled analgesia was continued for at least 72 h. Protocols were used to standardize perioperative medical management and to preserve masking intraoperatively and postoperatively. A uniform surveillance strategy was used for the identification of prospectively defined postoperative complications. Outcome evaluation included postoperative hospital length of stay, direct medical costs, selected postoperative morbidities, and postoperative recovery milestones.**

Results: **Length of stay and direct medical costs for patients surviving to discharge were similar among the four treatment groups. Postoperative outcomes were similar among the four treatment groups with respect to death, myocardial infarction, myocardial ischemia, reoperation, pneumonia, and renal failure. Epidural patient-controlled analgesia was associated with a significantly shorter time to extubation ($P = 0.002$). Times to intensive care unit discharge, ward admission, first bowel sounds, first flatus, tolerating clear liquids, tolerating regular diet, and independent ambulation were similar among the four treatment groups. Postoperative pain scores were also similar among the four treatment groups.**

Conclusions: **In patients undergoing surgery of the abdominal aorta, thoracic epidural anesthesia combined with a light general anesthesia and followed by either intravenous or epidural patient-controlled analgesia, offers no major advantage or disadvantage when compared with general anesthesia alone followed by either intravenous or epidural patient-controlled analgesia.**

This article is accompanied by an Editorial View. Please see: Todd MM: Clinical research manuscripts in ANESTHESIOLOGY. ANESTHESIOLOGY 2001; 95:1051–3.

THE most appropriate regimen of intraoperative anesthesia and postoperative analgesia for high-risk patients undergoing major vascular surgery is controversial. During the last decade, competing concerns regarding both the quality and the escalating costs of perioperative care have challenged clinicians to establish practice standards that are both safe and efficient.[1] Postoperative complications after moderate-risk elective surgery are common[2] and adversely impact clinical outcome, postoperative hospital length of stay (LOS), and resource use.[3]

Improvement in outcome and reduced use of medical resources in patients undergoing major vascular procedures may result from using epidural anesthesia and analgesia as compared with general anesthesia (GA) alone followed by intravenous opioid.[4,5] Investigations that support or refute such findings have suffered from deficiencies of design and methodology, including nonuniform patient population,[4,5] lack of standardization or control of perioperative treatments,[4–10] use of nonequivalent modalities for postoperative pain relief,[4–7,10] and possible investigator bias.[4–12] Bias is particularly difficult to avoid in clinical investigations of anesthetic techniques because management of perioperative physiologic changes and conduct of the technique itself have broad interclinician and intergroup variability. Clearly, masking of treating physicians to technique is a major challenge. At this time, it remains unknown whether regional anesthesia (alone or combined with GA) or analgesia offer any benefit in terms of improved patient outcome or reduced use of medical resources after vascular surgery. Furthermore, if regional techniques are in

* Associate Professor, § Assistant Professor, ## Professor, Department of Anesthesiology and Critical Care Medicine, ‡ Professor, ‖‖ Associate Professor, Department of Surgery, # Professor, Health Policy Management, ‡‡ Professor, Department of Medicine, The Johns Hopkins Medical Institutions. † Professor, Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee. ‖ Professor, Departments of Epidemiology and Biostatistics, §§ Assistant Professor, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland. ** Chairman, Department of Anesthesiology, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania. †† Staff Anesthesiologist, Greater Baltimore Medical Center, Baltimore, Maryland.

Received from the Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. Submitted for publication December 27, 2000. Accepted for publication May 25, 2001. Supported by grant No. GM 38177-08 from the National Institutes of Health, Bethesda, Maryland. Presented in part at the annual meeting of the Society of Cardiovascular Anesthesiologists, Chicago, Illinois, April 27, 1999.

Address reprint requests to Dr. Norris: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, 600 North Wolfe Street, Tower 711, Baltimore, Maryland 21287-8711. Address electronic mail to: enorris@jhmi.edu.

fact beneficial, it remains unknown whether the benefits reported are a result of specific features of either the intraoperative or postoperative technique or the combination of the two. Rigorously conducted clinical trials, comparing alternate combinations of intraoperative anesthesia and postoperative analgesia, are therefore necessary to establish the relation between anesthetic and analgesic techniques and important outcome variables.

To separate the influence of time period and technique, remove physician bias, and provide comparable perioperative care, we conducted a double-masked randomized clinical trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia with respect to LOS in patients undergoing surgery of the abdominal aorta. We also prospectively examined other outcomes, including direct medical costs, mortality, cardiac morbidity, and other selected perioperative morbidities. Because perioperative complications, whether surgical or medical, can be associated with expensive and prolonged hospitalizations, the choice of an appropriate anesthetic and analgesic regimen for patients at risk for perioperative morbidity is important to the patient, provider, payer, and society. The finding of a significant difference between the treatment groups would allow clinicians to optimize care with regard to both safety and economy, while a finding of no difference would allow choice based on physician or patient preference.

Methods

Patient Selection

The trial was approved by the Institutional Review Board, Joint Committee on Clinical Investigations of the Johns Hopkins Hospital (JHH; Baltimore, MD). The study group consisted of consenting patients undergoing abdominal aortic reconstructive surgery between August 1993 and July 1997. Prospective study candidates were identified from the elective surgery schedule. They were evaluated for eligibility and approached for consent 1–7 days before surgery. Procedures included elective abdominal aortic surgery for aneurysm or aortoiliac occlusive disease, as well as visceral and renal arterial reconstruction requiring abdominal aortic cross-clamping. Patients were excluded from study participation if their procedure required clamping of the thoracic aorta. Other exclusions included contraindication to any feature of the proposed clinical management, including epidural anesthesia, previous surgery or severe deformity of the thoraco-lumbar spine, previous or current neurologic disease affecting the lower hemithorax or below, opioid dependence, major surgery in the previous 14 days, and patient refusal.

Preoperative Management

Demographic data, medications, and surgical and medical history were obtained from the patient and medical record. Physical examination with blood pressure measurements in both upper extremities was performed in all patients. Patients were instructed in the use of a visual analog scale (VAS) and patient-controlled analgesia (PCA). Holter monitoring (Holter Monitor Model 90205; SpaceLabs Medical, Redmond, WA) was initiated the evening before or the morning of surgery and continued through the third postoperative day. Leads II and V5 were monitored continuously. Date and time of any lead position change were recorded throughout the monitoring period. All Holter tape recordings were subsequently analyzed using a computerized playback unit (Medical Analysis and Review Station Model 90103A-1ABG; SpaceLab Medical) and were reviewed by an experienced physician operator who was masked to the treatment regimen to which the patients had been assigned.

Patients consenting to enrollment were stratified by surgeon. Within strata, the treatment regimens were assigned according to a randomization scheme containing variable-sized, balanced blocks of treatment assignments. Patients were randomized to one of four treatment assignments: GA followed by intravenous PCA (IVPCA) (GA–IVPCA), GA followed by epidural PCA (EPCA) (GA–EPCA), regional supplemented GA (RSGA) followed by IVPCA (RSGA–IVPCA, and RSGA followed by EPCA (RSGA–EPCA). The evening before surgery, the JHH Investigational Pharmacy determined the patient's treatment assignment and prepared the masked study medications. On the morning of surgery, patients received their usual medications, except for oral hypoglycemics, and a sedative premedication of up to 10 mg diazepam administered orally. On arrival in the operating room, all patients were monitored with pulse oximetry, continuous multichannel electrocardiography, and noninvasive blood pressure. During insertion of intravascular and epidural catheters, patients were given intravenous midazolam in 0.5-mg increments (maximal dose of 5 mg) and fentanyl in 25-μg increments (maximum dose of 100 μg) for sedation. All patients underwent sequential placement of an intraarterial catheter in the arm with the highest preoperative blood pressure, thoracic epidural catheter, central venous catheter, and a pulmonary artery catheter. Thoracic epidural catheter placement was performed *via* the midline approach using a standard loss-of-resistance technique at the T8–T9 interspace for patients requiring a left flank incision, and at the T10–T11 interspace for patients requiring a midline incision. With the epidural needle bevel oriented in the cephalad direction, a uniport catheter was inserted 4 cm into the epidural space. All epidural catheters were tested for appropriate placement with the administration of a test dose consisting of 3 ml of 2% lidocaine with 15 μg of epinephrine. A bilateral, two or more–segment

objective sensory loss to pinprick was required for randomization. Formal entry into the study occurred after successful placement and testing of the epidural catheter. For reasons of patient safety, a sealed opaque envelope containing the randomized treatment assignment was kept with the patient in the operating room and intensive care unit (ICU) to permit immediate unmasking if patient condition warranted.

Anesthetic Management

All patients had GA induced. Each subject received 10–15 ml/kg of lactated Ringer's solution before induction, followed by incremental doses of sodium thiopental (up to 500 mg) and fentanyl (up to 250 μg, including sedation fentanyl) until unconsciousness was achieved. Anesthetic depth was deepened with enflurane, 0.1 mg/kg pancuronium was administered, and the trachea was intubated. GA was maintained using 50% nitrous oxide in oxygen and enflurane (0.2–0.8% end tidal). All patients received 500 ml of 6% hetastarch in saline (Hespan®; Braun Medical, Bethlehem, PA) over a period of 15 min after induction of GA. After induction of GA, the JHH Investigational Pharmacy delivered the masked study medications to the operating room. During positioning and at least 15 min before skin incision, all patients received both masked epidural and intravenous bolus doses followed by masked continuous epidural and intravenous infusions (Baxter Auto Syringe Infusion Pump Model AS40A; Baxter, Deerfield, IL) specific to their intraoperative treatment assignment (GA or RSGA; Appendix 1).

Throughout the intraoperative period, our hemodynamic goal was to maintain a heart rate of 40–85 beats/min and a mean arterial pressure (MAP) within limits established preoperatively and independent of the type of anesthesia used. Upper and lower limits for MAP were determined before randomization for each patient using a nomogram (fig. 1) modified from that used in a previous clinical trial.[11] During the surgery, all patients received simultaneous adjustments of their intravenous and epidural infusion rates in response to need according to protocol (Appendix 2).

Fluid and blood administration, as well as urine output maintenance, were managed according to protocol (Appendix 3). All patients received a forced warm-air blanket over the upper body and warmed fluids throughout the operative procedure. The incisional approach (left flank or midline) for aortic reconstruction was predetermined, and the site of epidural placement was adjusted as described. All patients received heparin (100 units/kg) before aortic cross-clamping. Additional heparin dosing and reversal with protamine occurred by protocol. All patients received antibiotics before skin incision and for 24 h postoperatively.

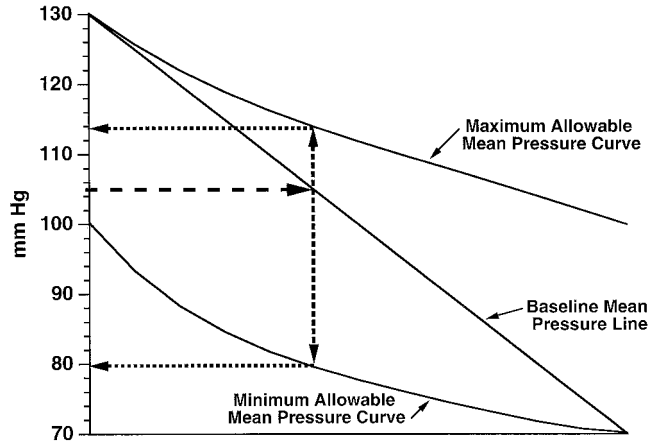

Fig. 1. Nomogram used to determine minimum and maximum mean blood pressure limits. The nomogram is used by reading the baseline mean arterial pressure (MAP) from the left-handed axis horizontally onto the diagonal baseline mean pressure line. The point of intersection on this line is then extended vertically to intersect with the minimum and maximum allowable mean pressure curves. Thus, a patient with a baseline MAP of 105 mmHg, shown in the figure, would have an allowable MAP range of 80–114 mmHg. Baseline MAP was defined as the median of three preoperative MAPs obtained by: (1) nursing staff on hospital admission; (2) study physician during preoperative examination; and (3) intraarterial catheter immediately after placement in the operating room.

Postoperative Management

At the start of wound closure, enflurane and the masked epidural and intravenous infusions were discontinued, and masked postoperative pain management (Appendix 4) was initiated. Immediate postoperative extubation was not planned. Instead, our protocols facilitated stability and preservation of masking. All patients received 250 μg fentanyl (open label) and 5 mg of midazolam intravenously during wound closure. Neuromuscular blockade was not reversed intraoperatively. All patients received a masked postoperative epidural bolus at the start of wound closure that varied based on both intraoperative anesthetic and postoperative analgesic regimens (Appendix 4). This variation was necessary to account for the different dynamics associated with the transition from each of the intraoperative techniques to each of the postoperative techniques and to preserve masking. After administration of the masked epidural bolus, a masked "double pump" (Bard Ambulatory PCA Pump; Bard, Andover, MA) set-up with a single PCA button to activate both epidural and intravenous pumps was initiated. The masked postoperative PCA regimen was continued for at least 72 h postoperatively and was directly supervised by an anesthesiology-based acute pain service. All aspects of the masked postoperative PCA regimen were controlled by protocol (Appendix 4). Patients were evaluated by the acute pain service on arrival to the ICU, 2 and 6 h after ICU arrival, 3 times daily (7 AM, 1 PM, and 7 PM) for the first 3 postoperative days, and daily through postoperative day 7. Pain scores, least pain since last assessment (VAS-least), pain now

(VAS-now), and pain with vigorous cough (VAS-cough) were obtained three times daily (7 AM, 1 PM, and 7 PM) for the first 3 postoperative days and daily through postoperative day 7. Postoperative pain was assessed using a 100-mm VAS with 0 and 10 labeled as "no pain" and "worst pain possible," respectively.

All patients were placed on mechanical ventilator support on arrival to the ICU. Weaning from mechanical ventilation was initiated when rectal temperature was greater than or equal to 36°C, there was no evidence of active bleeding, fluid requirement was less than 250 ml/h, and the patient was able to follow simple commands. Weaning from mechanical ventilation and extubation were controlled by protocol based on pulse oximetry, end-tidal carbon dioxide monitoring, and arterial blood gases. Intraoperative MAP limits were continued during the ICU stay. Heart rate was maintained between 40 and 90 beats/min in the ICU. All patients remained in the ICU for a minimum of 24 h. Discharge of patients from the ICU was determined at the discretion of the ICU attending physician and was dependent on the assessment of the overall patient course and cardiopulmonary stability. Patients were admitted to the regular surgical ward only when they did not require invasive monitoring, vasoactive infusions, fluid administration greater than maintenance concentrations, or aggressive pulmonary therapy for at least 12 h. Patients requiring reoperation during the initial 72 h postoperatively received GA using 50% nitrous oxide, low-dose enflurane, and muscle relaxants as needed. When in place, the masked postoperative analgesic regimens were continued during reoperation. No additional local anesthetics were administered *via* the epidural catheter for reoperation.

Postoperative feeding and ambulation followed goals established prospectively by the surgical team. These goals included the following: (1) nasogastric tube removal with return of bowel sounds; (2) clear liquid diet initiated within 24 h after nasogastric tube removal; (3) advancement to regular diet within 24 h after tolerating clear liquids; (4) out-of-bed to a chair within 24 h after extubation; and (5) assisted ambulation initiated within 48 h after extubation. Requirements for hospital discharge included the following: (1) afebrile with stable vital signs for 24 h; (2) tolerating regular diet for 24 h (3) baseline bladder and bowel activity; (4) good pain control on oral analgesics; and (5) independent ambulation, if possible.

Patients were examined and interviewed at 30 min and 2 h after arrival in the ICU, daily for the first 7 postoperative days, and on the day of discharge. Medical charts were reviewed daily until discharge.

Clinical Outcome Analysis

Length of stay, the primary outcome variable, was defined as the postoperative hospital LOS and calculated using date of surgery and date of hospital discharge. Major secondary outcomes included direct medical costs, hospital mortality, and major cardiac morbidity. Direct medical costs were defined as the sum of the in-patient hospital costs and physician costs (see below). Hospital mortality was defined as any death occurring during the postoperative hospitalization. Major cardiac morbidity was defined as cardiac death, nonfatal myocardial infarction (MI), and unstable angina. These morbidities were determined by a cardiologist (S. C. A.) masked to the anesthetic and analgesic regimens based on the following information: (1) 12-lead electrocardiogram obtained preoperatively, postoperatively on the day of surgery, and on postoperative days 1, 2, 3, and 7; (2) total creatinine phosphokinase and MB isoenzymes drawn at 6-h intervals for the first 24 h, then daily through postoperative day 3; and (3) chest pain information obtained daily for the first 7 postoperative days. Ischemic electrocardiogram changes, chest pain, or clinical indicators of ischemia (such as congestive symptoms or arrhythmia) during the first 7 postoperative days resulted in serial electrocardiograms and creatinine phosphokinase with MB isoenzymes for 24 h. Electrocardiogram abnormalities were diagnosed using the Minnesota Code.[13] Cardiac death was defined as any death secondary to MI, congestive heart failure (CHF), or arrhythmia. The cardiologist was given information from autopsy, death certificate, and medical consultations. The diagnosis of MI required new Q waves of at least 0.04-s duration and a minimum of 1-mm depth on 12-lead electrocardiogram, or ischemic electrocardiogram changes associated with an increase in creatinine phosphokinase with a greater than 5% MB fraction. Unstable angina was defined as recurrent ischemic cardiac pain at rest with ECG changes occurring at least twice during medical therapy. All of the above cardiac outcomes were diagnosed based on the patients' first 7 postoperative days.

Other cardiac outcomes considered included myocardial ischemia, CHF, and ventricular tachyarrhythmia. Myocardial ischemia was defined as reversible ST depression (downward or horizontal sloping) greater than or equal to 1 mm below baseline or ST elevation greater than or equal to 2 mm above baseline in at least one lead, lasting 60 s or more, and documented by continuous Holter monitoring. CHF was defined as a clinical diagnosis based on the presence of rales, increased pulmonary capillary wedge pressure, S_3 gallop, classic chest radiograph findings, and requiring intervention with inotropes or venodilators. Chest radiograph findings without clinical signs were not diagnosed as CHF. Ventricular tachyarrhythmia was defined as documented ventricular fibrillation or ventricular tachycardia. Cardiac outcomes that appeared subsequent to MI were not considered separate events.

Other secondary outcomes considered included major surgical complication, acute respiratory failure, readmis-

sion to the ICU, major infection, renal failure, and neurologic deficit. Major surgical complication was defined as reoperation or bowel ischemia. Bowel ischemia required conformation by endoscopy or laparotomy. Acute respiratory failure was defined as either mechanical ventilation for more than 24 h postoperatively or need for reintubation and mechanical ventilation. Readmission to the ICU was defined as any return to the ICU after discharge. Major infection was defined as either pneumonia or sepsis. Pneumonia was defined as a new infiltrate on chest radiograph combined with the appearance of two of the following conditions within 24 h of the radiologic abnormality: temperature greater than 38.5°C, leukocyte count greater than 10,000, or the identification of a pathogen by sputum gram stain or culture. Treatment with an antibiotic was required for the diagnosis of pneumonia. Sepsis was defined as a localized, culture-positive infection with a leukocyte count greater than 10,000 and one or more of the following conditions: clinical evidence of bacteremia with chills and fever; positive blood culture with the same pathogen found in the original culture; or hemodynamic parameters consistent with sepsis, *i.e.*, high cardiac output and low systemic vascular resistance within 24 h of having a temperature greater than 38.5°C. Renal failure was defined as any postoperative increase in serum creatinine of 2.0 mg/dl or greater. Neurologic deficit was defined as any new focal neurologic deficit.

Additional secondary outcomes included postoperative recovery milestones (time to extubation; LOS in the ICU; LOS in a monitored care setting; time to first bowel sounds, flatus and bowel movement; time to tolerating clear liquids and regular diet; time to independent ambulation) and pain scores.

Direct Medical Costs

In-patient hospital and physician charges that were incurred from the operative day until the day of discharge were obtained for each patient using the JHH billing information. The methods developed by Lave *et al.*[14] were used to convert hospital and physician charges to costs. The Maryland Health Services Cost Review Commission cost-to-charge ratio for the JHH (0.785) was used to convert in-patient charges to costs. Physician billing data included charges, Current Procedural Terminology codes, and the amount paid. Costs for each Current Procedural Terminology code were estimated using Medicare Resource Based Relative Value Scale fee schedules. Where Current Procedural Terminology codes were not listed in the Resource Based Relative Value Scale file, the amount paid was used ($< 3\%$ of encounters). To remove the effects of price inflation, costs were adjusted to 1997 dollars using Consumer Price Indexes of Medical Care Prices from the US Bureau of Labor Statistics. Patients were not charged for acute pain service or pharmacy activities related to their masked intraoperative and postoperative treatments.

Follow-up

Patients were contacted by telephone at 1, 3, 6, and 12 months after discharge from the hospital. Relatives of patients who could not be located were contacted to determine if the patient had died. Death certificates were obtained to verify deaths during the follow-up period.

Study Population Size

The study population size for this trial was 204 patients. Based on a review of 234 consecutive patients undergoing abdominal aortic reconstruction at the JHH, we found a mean LOS of 12.7 days (SD = 4.5). We considered a 2.5-day reduction (20%) in LOS to be both clinically and economically important. Based on the formula for normal theory and assuming a two-sided type I error protection of 0.05 and a power of 0.80, 51 patients in each of the four groups were required to reveal a reduction in mean LOS of 2.5 days in any group.

Clinical Trial Monitoring

After patient enrollment was initiated, a clinical trial monitoring committee was convened at 6–12-month intervals to examine accumulated data and determine whether it was ethically and scientifically appropriate to continue to randomize patients. The committee consisted of specialists (surgery, cardiology, cardiac anesthesia, epidemiology, biostatistics, and medical ethics) not involved in the conduct of the trial. The committee met four times during the course of the trial and examined data on 156 patients during the last meeting. Conditional power analysis at that time resulted in an estimated conditional power of 0.6%, indicating a 0.6% chance of detecting a statistically significant difference in LOS among the treatment groups if the trial was continued to the planned recruitment of 204 subjects. Based on this conditional power analysis, as well as the lack of evidence of any apparent benefit of RSGA or EPCA, the committee recommended that the trial be terminated. The trial was therefore stopped after 168 patients were randomized.

Statistical Analysis

Statistical analysis was performed on a personal computer with SAS software (version 6.12; SAS Institute Inc., Cary, NC). All analyses were performed by assigned treatment (intent to treat). Numerous treatment comparisons were performed as follows: (1) among all four treatment groups (GA–IVPCA, RSGA–IVPCA, GA–EPCA, and RSGA–EPCA); (2) between the two intraoperative treatments (GA and RSGA); (3) between the two postoperative treatments (IVPCA and EPCA); and (4) between the group with no epidural activation (GA–

IVPCA) and the remaining three groups with epidural activation (RSGA–IVPCA, GA–EPCA, and RSGA–EPCA). In addition, a factorial analysis was conducted that involved simultaneous consideration of both intraoperative and postoperative treatment, *i.e.*, both treatments were included in the same statistical model. This allowed the effect of postoperative analgesia to be examined, having adjusted for intraoperative anesthesia, and *vice versa*. The factorial study design permits such analysis to assess the independent effects of the two sets of treatments administered to the same patient.

Univariate associations of categoric variables with treatment were analyzed with the chi-square test of independence or the Fisher exact test when the chi-square test was not valid because of small numbers. Continuous variables were analyzed by treatment group with linear regression of the ranks of the variables to decrease the influence of outliers. Mean values and SDs are reported for continuous variables that are approximately normally distributed; for continuous variables that are not normally distributed, the median and resistant SD, calculated as the interquartile range divided by 1.349,[15] are reported. Multivariate logistic regression and ranked linear regression were used, respectively, for categoric and continuous variables in analyses adjusting for baseline differences among the treatment groups.

Results

Patient Population and Intraoperative Variables

Three hundred nine consecutive patients were evaluated for study participation, and 168 patients were randomized (fig. 2). Epidural catheters were repositioned (n = 1) or replaced (n = 4) for evidence of intravascular placement (n = 3) or lack of objective sensory loss to pinprick (n = 2) and retested. Seven consented patients were not randomized because of inability to place an epidural catheter at the desired level. Eight patients (two in each group) were studied as part of a pilot phase. Only mortality data includes pilot patients. The treatment groups had similar baseline characteristics (table 1).

Intraoperative data by anesthesia treatment assignment (GA or RSGA) for patients surviving to discharge are summarized in table 2. Surgical approach, clamp level, surgical procedure, MAP limits, fluid administration, and urine output were similar between the two intraoperative groups. Total operating room time ($P = 0.012$), operative time ($P = 0.003$), and aortic cross-clamp time ($P = 0.048$) were significantly longer in the RSGA group as compared with the GA group (table 2). Two patients with uncontrolled surgical bleeding required discontinuance of the intraoperative protocols because of hemodynamic instability; both of these patients died on the day of surgery. No patient required any deviation from the masked intraoperative protocols because of inadequate anesthesia. Intraoperative treatment assignment was unmasked in one patient because of inadvertent entry into the bowel and subsequent postponement of aortic surgery (randomized to RSGA–EPCA).

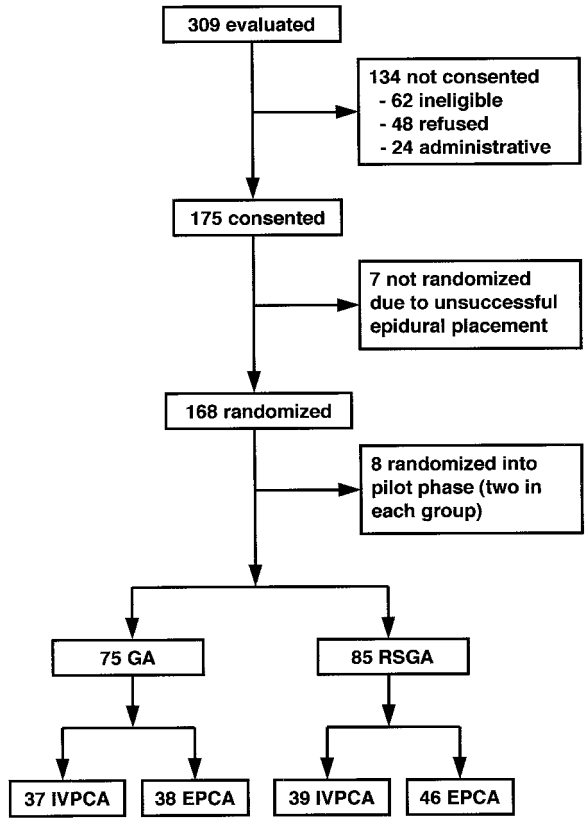

Fig. 2. Diagrammatic representation of the patient distribution. GA = general anesthesia; RSGA = regional supplemented general anesthesia; IVPCA = intravenous patient-controlled analgesia; EPCA = epidural patient-controlled analgesia.

Postoperative Variables

The postoperative course for patients surviving to discharge is summarized in table 3. Time to extubation was significantly shorter in the GA–EPCA ($P = 0.030$) and RSGA–EPCA ($P = 0.002$) groups as compared with the GA–IVPCA group. In the factorial analysis, EPCA, but not RSGA, was associated with a significantly shorter time to extubation ($P = 0.002$). Time to first bowel movement approached statistical significance ($P = 0.051$) with shorter times in the GA–IVPCA and RSGA–IVPCA groups relative to the GA–EPCA and RSGA–EPCA groups (table 3). There were no significant differences among the four treatment groups in the times to ICU discharge, ward admission, first bowel sounds, first flatus, tolerating clear liquids, tolerating regular diet, or independent ambulation (table 3).

Time to discontinuation of the masked PCA regimens was not different among the four treatment groups (table 3). PCA was not initiated in one patient (0.6%) surviving to discharge because of massive intraoperative surgical bleeding and hemodynamic instability (random-

Table 1. Baseline Clinical Characteristics by Treatment Assignment

	GA–IVPCA	RSGA–IVPCA	GA–EPCA	RSGA–EPCA	*P*
No. of patients	37	39	38	46	
Age (yr)*	70 (9.5)	67 (10)	68 (9.9)	68 (8.4)	0.706
Males	78	69	63	77	0.540
Weight (kg)*	80 (18)	75 (15)	74 (14)	77 (15)	0.565
Abdominal aortic aneurysm	78	74	76	67	0.636
Diabetes requiring medication	3	5	3	7	0.841
Renal insufficiency	19	23	24	28	0.752
Smoking	84	92	92	91	0.609
Cardiovascular history					
Hypertension	60	60	68	63	0.819
Angina	41	36	34	33	0.895
Congestive heart failure	6	18	5	17	0.138
Myocardial infarction	15	33	27	30	0.298
CABG	19	31	18	24	0.544
PTCA	11	10	11	17	0.755
Stroke	16	10	5	11	0.516
Previous vascular surgery	14	15	16	15	0.990
Preoperative medications					
Long-acting nitrates	11	13	0	4	0.071
Converting enzyme inhibitor	24	21	16	20	0.834
Calcium channel blocker	38	39	45	37	0.892
β blocker	27	33	16	28	0.352
Other antihypertensive agents	8	10	16	24	0.175
Diuretic	22	18	16	28	0.515
Digoxin	11	10	16	13	0.881
Aspirin	24	37	34	35	0.658
Laboratory analysis*					
Hematocrit (%)	41 (5.4)	39 (5.6)	40 (4.3)	40 (5.4)	0.650
Creatinine (mg/dL)	1.4 (1.6)	1.6 (1.6)	1.3 (0.7)	1.4 (1.0)	0.788

All data are represented as percentages except for age, weight, hematocrit, and creatinine.

* Values are mean (SD).

GA–IVPCA = general anesthesia and intravenous patient-controlled analgesia; RSGA–IVPCA = regional supplemented general anesthesia and intravenous patient-controlled analgesia; GA–EPCA = general anesthesia and epidural patient-controlled analgesia; RSGA–EPCA = regional supplemented general anesthesia and epidural patient-controlled analgesia; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.

ized to RSGA–EPCA). Four patients (2.6%) surviving to discharge had their masked PCA regimens discontinued within 24 h because of the following reasons: (1) hypotension requiring vasopressor support (randomized to RSGA–EPCA); (2) reoperation (randomized to GA–EPCA); (3) broken catheter during transport to ICU (randomized to RSGA–IVPCA); and (4) massive surgical bleeding with hemodynamic instability (randomized to GA–IVPCA). One patient (0.6%) required discontinuance of the masked PCA regimen at 38 h because of inadequate pain control (randomized to GA–EPCA). Two patients (1.3%) surviving to discharge required unmasking of their treatment assignment postoperatively because of hypotension requiring vasopressor support on postoperative day 1 (randomized to RSGA–EPCA) and orthostatic hypotension on postoperative day 2 (randomized to RSGA–EPCA).

There were no differences in VAS pain scores over time among the four treatment groups for VAS-least pain ($P = 0.867$), VAS-now pain ($P = 0.992$), or VAS-cough pain ($P = 0.488$). The mean difference over time between VAS-least pain and VAS-now pain for the entire cohort was 9.5 mm (95% confidence interval, 7.5–11.4 mm). The mean difference over time between VAS-now pain and VAS-cough pain for the entire cohort was 28.6 mm (95% confidence interval, 25.9–31.3 mm).

Mortality and Major Morbidity

Hospital mortality, cardiac death, and mortality at 12 months were not different among the four treatment groups (table 4). Nine deaths (5.4%) occurred during hospitalization. One patient (0.6%) assigned to GA–EPCA died of a cardiac death on postoperative day 6. Three patients (1.8%) died within the 12-month follow-up period.

Major morbidity for patients surviving to discharge is summarized in table 5; no significant difference was observed among the four treatment groups. Five patients (3.3%) had nonfatal MI within 7 days of surgery. All MIs occurred on postoperative day 2 or 3. No MIs were diagnosed during the first 7 postoperative days for any of the patients who did not survive to hospital discharge. One patient (0.7%) assigned to RSGA–IVPCA had CHF. Twenty-four patients (15.9%) had 104 episodes of Holter-documented myocardial ischemia. Of these 104 episodes, 11 occurred in 7 patients before randomiza-

Table 2. Intraoperative Data by Anesthesia Treatment for Patients Surviving to Discharge

	GA	RSGA	*P*
No. of patients	71	80	
Surgical approach*			0.703
Transperitoneal	39	42	
Retroperitoneal	61	58	
Clamp level*			0.318
Supraceliac	10	14	
Suprarenal	3	8	
Infrarenal	87	78	
Surgical procedure*			0.538
Aortic tube graft	38	29	
Aortic bifurcated graft	37	46	
Aortic graft and bypass	14	16	
Other	11	9	
Mean arterial blood pressure limits†			
Maximum (mmHg)	111 (9.8)	113 (7.2)	0.402
Minimum (mmHg)	81 (9.8)	80 (6.5)	0.686
OR time (h)†	5.6 (1.4)	6.1 (1.6)	0.012
Anesthesia start-up (h)	1.3 (0.3)	1.4 (0.4)	0.253
Operative time (h)	3.6 (1.4)	4.2 (1.5)	0.003
Cross-clamp time (min)	75 (34)	90 (44)	0.048
Blood loss (ml)‡	1,500 (1,112)	1,500 (1,019)	0.594
Fluids‡			
PRBCs (units)	2.0 (1.5)	2.0 (2.2)	0.179
Cellsaver (ml)	425 (352)	338 (361)	0.963
Crystalloid (ml/h)	1,037 (272)	1,045 (313)	0.406
Colloid (ml/h)	116 (90)	140 (82)	0.534
Urine output (ml/h)‡	99 (63)	101 (73)	0.391

* Data are represented as percentages. † Values are mean (SD). ‡ Values are median ($SD_{resistant}$).

GA = general anesthesia; RSGA = regional supplemented general anesthesia.

tion. Perioperative Holter ischemia was predictive of postoperative MI, with 3 of 24 patients who had ischemia (12.5%) and only 2 of 127 patients who did not have ischemia (1.6%; $P = 0.029$) having MI. One patient who did not survive to hospital discharge had two episodes of Holter ischemia. Pneumonia was diagnosed in 2 patients (1.3%), prolonged intubation occurred in 23 patients (15.2%), and 3 patients (2.0%) required reintubation. Renal failure occurred in four patients (2.6%), sepsis in two patients (1.3%), and neurologic deficit in two patients (1.3%). Twelve patients (7.9%) required reoperation, and six patients (4.0%) required readmission to the ICU.

Length of Stay and Cost

Length-of-stay data for patients surviving to discharge are shown in table 6; no significant difference was observed among the four treatment groups ($P = 0.833$). Median LOS for all patients surviving to discharge was 7.0 days: 7.0 in the GA–IVPCA group, 8.0 in the RSGA–IVPCA group, 7.0 in the GA–EPCA group, and 7.0 in the RSGA–EPCA group. No significant difference in LOS was observed between intraoperative treatment groups (GA *vs.* RSGA; $P = 0.416$), postoperative treatment groups (IVPCA *vs.* EPCA; $P = 0.673$), epidural activation (GA–IVPCA *vs.* RSGA–IVPCA, RSGA–EPCA, and GA–EPCA; $P = 0.854$), or in the factorial analysis ($P = 0.648$). Median LOS for patients who did not survive to discharge was 3 days (mean, 8.8 days). LOS was significantly less for patients who were accrued during the last 24 months of the trial (median LOS, 7 days) as compared with the first 24 months (median LOS, 8 days) ($P = 0.005$). However, no significant difference was observed in LOS among the four treatment groups during these two recruitment periods ($P = 0.948$). Incisional approach (left flank or midline) was not associated with LOS ($P = 0.151$), nor did it affect the lack of association between the four treatment groups and LOS ($P = 0.836$).

Direct medical costs for patients surviving to discharge are shown in table 6. Median direct medical cost for all patients surviving to discharge was \$22,674 ($SD_{resistant}$ = \$4,903). In-patient, physician, and total direct medical costs were similar among the four treatment groups (table 6).

The overall rate of missing data was less than 1% for the entire study population. No patient was lost to follow-up.

Discussion

To our knowledge, this investigation is the first double-masked randomized clinical trial evaluating alternate combinations of intraoperative anesthesia (GA alone or RSGA) and postoperative analgesia (IVPCA or EPCA) for any operative procedure. The major finding of this investigation is that, in patients undergoing surgery of the abdominal aorta, thoracic epidural anesthesia combined with a light GA and followed by either IVPCA or EPCA offers no major advantage or disadvantage when compared with GA alone followed by either IVPCA or EPCA. Specifically, our results suggest that thoracic epidural anesthesia or analgesia for abdominal aortic surgery does not significantly affect LOS, direct medical costs, mortality, major cardiac morbidity, or perioperative morbidity. These conclusions remain valid whether the data are analyzed by intraoperative treatment, postoperative treatment, any epidural activation perioperatively, or factorial analysis. Based on the results of a conditional power analysis (see above) and the lack of apparent clinical benefit of RSGA or EPCA, the clinical trial monitoring committee recommended early termination of the trial.

Methodology

Features of this trial are the standardization of clinical care throughout the perioperative period, inclusion of all four combinations of intraoperative anesthesia and postoperative analgesia, and masking of both patient and treating physician to both intraoperative and postoperative treatments. In addition, we used a uniform surveil-

Table 3. Postoperative Data by Treatment Assignment for Patients Surviving to Discharge

	GA–IVPCA	RSGA–IVPCA	GA–EPCA	RSGA–EPCA	*P*
No. of patients	35	36	36	44	
Hours to					
Extubation	19 (7)	19 (10)	16 (6)	13 (8)	0.010
ICU discharge	46 (9)	43 (29)	43 (29)	43 (17)	0.424
Admission to ward	70 (39)	66 (40)	53 (35)	49 (20)	0.196
First bowel sounds	26 (21)	30 (19)	25 (17)	21 (14)	0.421
First flatus	54 (19)	58 (22)	54 (20)	52 (29)	0.666
First bowel movement	93 (44)	90 (32)	113 (42)	117 (42)	0.051
Tolerating clear liquids	68 (28)	67 (30)	69 (21)	69 (40)	0.923
Tolerating regular diet	111 (35)	113 (47)	108 (21)	102 (45)	0.907
Independent ambulation	94 (33)	85 (46)	92 (31)	89 (34)	0.814
PCA discontinuation	81 (13)	78 (14)	78 (16)	79 (13)	0.523

Values are median ($SD_{resistant}$).

GA–IVPCA = general anesthesia and intravenous patient-controlled analgesia; RSGA–IVPCA = regional supplemented general anesthesia and intravenous patient-controlled analgesia; GA–EPCA = general anesthesia and epidural patient-controlled analgesia; RSGA–EPCA = regional supplemented general anesthesia and epidural patient-controlled analgesia; PCA = patient-controlled analgesia; ICU = intensive care unit.

lance strategy for the identification of prospectively defined postoperative outcomes.

Restricting the patient population to a uniformly stressful surgical procedure (abdominal aortic reconstruction) and standardizing perioperative management were important aspects of the study design. They reduced the number of confounding variables and reduced the likelihood of unrevealed aspects of patient management impacting outcome (*i.e.*, improved the likelihood of implicating the anesthetic or analgesic technique). Our previous clinical trial in patients undergoing lower extremity vascular surgery (randomized to either epidural anesthesia followed by epidural analgesia or GA followed by IVPCA) found no difference in overall incidence of death, major cardiac morbidity, myocardial ischemia, respiratory failure, renal failure, or major infection.[11] In addition, we did not find a difference in LOS attributable to anesthetic technique. However, the overall rate of morbidity was low; therefore, it was not surprising that no significant difference was found between treatment groups with respect to these outcomes. The current trial was designed to include similar risk patients undergoing a more stressful operative procedure. We hypothesized that a greater surgical stress would lead to a higher incidence of postoperative morbidity, which might thereby identify a difference in LOS attributable to the type of anesthesia or analgesia.

The factorial design of this trial allowed for the inclusion of all four possible combinations of intraoperative anesthesia and postoperative analgesia and the ability to separate the influences of time period and technique. This design allows for outcome analysis by treatment group, intraoperative treatment, postoperative treatment, any epidural activation, and simultaneous consideration of both intraoperative and postoperative treatments in the same model (factorial analysis). Therefore, the factorial design allows for improvement in outcome to be attributed to the intraoperative anesthesia, postoperative analgesia, the combination of the two, or to other unrelated factors. Our results do not support the conclusions of previous studies suggesting that postoperative epidural analgesia rather than intraoperative epidural anesthesia is the factor responsible for improved perioperative outcome.[5,6]

Randomized trials evaluating the value of regional techniques for high-risk patients undergoing major vascular procedures have focused primarily on relatively rare events (death and MI) or intermediate events (myocardial ischemia and CHF) with an unknown relation to outcomes meaningful to patients (return to functional status, quality of life) or society (LOS, healthcare cost).[5–7,9–12] Although these trials have not conclusively established any improvement in outcome related to the use of regional techniques perioperatively, they suffered from the design and methodology limitations as described above. Therefore, if rigorously conducted clinical trials are to uncover a benefit

Table 4. Death after Randomization by Treatment Assignment

	GA–IVPCA	RSGA–IVPCA	GA–EPCA	RSGA–EPCA	Total	*P*
No. of patients	39	41	40	48	168	
Death during hospital stay	2 (5.1)	3 (7.3)	2 (5.0)	2 (4.2)	9 (5.4)	0.965
Cardiac death	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.6)	0.470
Mortality at 12 months	4 (10)	4 (9.8)	2 (5.0)	2 (4.4)	12 (7.1)	0.635

Percentages are given in parentheses.

GA–IVPCA = general anesthesia and intravenous patient-controlled analgesia; RSGA–IVPCA = regional supplemented general anesthesia and intravenous patient-controlled analgesia; GA–EPCA = general anesthesia and epidural patient-controlled analgesia; RSGA–EPCA = regional supplemented general anesthesia and epidural patient-controlled analgesia.

Table 5. Major Morbidity by Treatment Assignment for Patients Surviving to Discharge

	GA–IVPCA	RSGA–IVPCA	GA–EPCA	RSGA–EPCA	*P*
No. of patients	35	36	36	44	
Nonfatal myocardial infarction	0 (0.0)	2 (5.6)	2 (5.6)	1 (2.3)	0.556
Unstable angina	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Congestive heart failure	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0.707
Ventricular tachyarrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Holter ischemia*	6 (17)	3 (8.3)	7 (19)	8 (18)	0.554
Reintubation	1 (2.9)	1 (2.8)	0 (0.0)	1 (2.3)	0.899
Prolonged intubation	6 (17)	8 (22)	6 (17)	3 (6.8)	0.269
Pneumonia	0 (0.0)	1 (2.8)	1 (2.8)	0 (0.0)	0.578
Bowel ischemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Sepsis	1 (2.9)	0 (0.0)	0 (0.0)	1 (2.3)	0.720
Reoperation	2 (5.7)	2 (5.6)	3 (8.3)	4 (9.1)	0.926
Readmission to ICU	2 (5.7)	2 (5.6)	0 (0.0)	2 (4.5)	0.586
Renal failure	2 (5.7)	1 (2.8)	0 (0.0)	1 (2.3)	0.542
Neurologic deficit	1 (2.9)	0 (0.0)	1 (2.8)	0 (0.0)	0.470

Percentages are given in parentheses.

* Includes preoperative monitoring.

GA–IVPCA = general anesthesia and intravenous patient-controlled analgesia; RSGA–IVPCA = regional supplemented general anesthesia and intravenous patient-controlled analgesia; GA–EPCA = general anesthesia and epidural patient-controlled analgesia; RSGA–EPCA = regional supplemented general anesthesia and epidural patient-controlled analgesia; ICU = intensive care unit.

related to regional techniques perioperatively (assuming such a benefit exists), efforts need to be refocused on important health outcomes related to LOS, functional status, healthcare cost, and quality of life.

Length of Stay and Cost

The primary outcome used in this trial was LOS. The duration and intensity of postoperative care after major elective surgery is critically dependent on the physiologic derangements incurred during the perioperative period (depressed level of consciousness, hypothermia, fluid overload, incisional pain, ileus and respiratory depression), and the development of certain less common, but more severe, postoperative complications (MI, CHF, pneumonia, sepsis, renal failure, bleeding and decreased tissue perfusion). LOS was therefore considered to be the single outcome variable most directly proportional to an integrated final negative effect of all significant perioperative morbidity (neglecting in-hospital death) and the variable most likely to be altered by anesthetic or analgesic technique. The number of patients to be included in this investigation was prospectively established from a review of 234 consecutive patients undergoing abdominal aortic reconstruction at our institution. We believed that a 2.5-day reduction (20%) in LOS was both clinically and economically significant and based our sample size on such a reduction. The chosen value of 2.5 days was determined based on a consensus opinion (investigators, anesthesiologists, surgeons, and health economists) at our institution that this LOS benefit of treatment would result in clinicians changing their practice or recommending the technique to their patients. Importantly, this LOS benefit resulted in a sample size (a total of 204 patients) that was feasible for a single-site study. A smaller or larger LOS benefit would have significantly affected our clinical trial sample-size calculation.[16]

Median LOS for all 151 patients surviving to discharge was 7.0 days (mean, 8.8 days) and was similar among the four treatment groups. As noted, our study design also allowed LOS to be evaluated by intraoperative anesthetic technique, postoperative analgesic technique, epidural

Table 6. Duration of Stay and Direct Medical Costs by Treatment Assignment for Patients Surviving to Discharge

	GA–IVPCA	RSGA–IVPCA	GA–EPCA	RSGA–EPCA	Total	*P*
No. of patients	35	36	36	44	151	—
Duration of stay (days)	7.0 (2.2)	8.0 (2.8)	7.0 (2.0)	7.0 (2.8)	7.0 (2.2)	0.833
Range	4–43	5–28	5–20	5–18	4–43	—
95% CI	7.0–13.3	7.4–10.2	6.9–8.8	7.6–9.6	7.9–9.7	—
Direct medical costs (1997 $)						
Inpatient	12,413 (2867)	13,786 (4413)	12,492 (3111)	13,767 (3900)	12,793 (3777)	0.242
Physician	10,394 (5993)	10,288 (4536)	9,609 (3866)	9,790 (3567)	9,934 (4072)	0.459
Total	22,674 (8783)	23,001 (6079)	22,182 (3914)	22,727 (3961)	22,674 (4903)	0.851

Values are median ($SD_{resistant}$).

GA–IVPCA = general anesthesia and intravenous patient-controlled analgesia; RSGA–IVPCA = regional supplemented general anesthesia and intravenous patient-controlled analgesia; GA–EPCA = general anesthesia and epidural patient-controlled analgesia; RSGA–EPCA = regional supplemented general anesthesia and epidural patient-controlled analgesia; PCA = patient-controlled analgesia.

activation, and factorial analysis. LOS was similar among or between groups in each of these circumstances.

Our overall LOS was lower in this trial than in other recent studies of patients undergoing elective abdominal aortic reconstruction.[6,8,9,12] Baron *et al.*[6] evaluated 167 patients randomized to either RSGA or GA alone and reported a mean LOS greater than 15 days in each group. Davies *et al.*[9] reported on 50 patients randomized to either RSGA followed by continuous epidural analgesia or GA followed by intravenous morphine infusion and reported a mean LOS of 16 days in each group. Bois *et al.*[12] reported on 114 patients randomized to intravenous morphine PCA or continuous thoracic epidural analgesia after GA and reported a mean LOS of 14 and 16 days, respectively. Finally, Boylan *et al.*[8] reported on 40 patients randomized to RSGA followed by continuous epidural analgesia or GA followed by IVPCA and reported a median LOS of 13 and 14 days, respectively. A recent population-based study reported a mean LOS of 11 days for 2,335 elective abdominal aortic aneurysm repairs in Maryland.[17] Using the National Hospital Discharge Survey, the largest dataset on hospitalizations in the US, Lawrence *et al.*[18] also reported a mean LOS of 11 days for 32,389 patients who underwent elective abdominal aortic aneurysm repair in 1994. Although no difference in LOS attributable to anesthetic or analgesic treatment was found in this trial, there was an overall 31% reduction in mean LOS compared with historical controls at our institution (12.7 *vs.* 8.8 days). This lower-than-expected LOS made the reduction of 2.5 days (hypothesized effect) in any treatment group unlikely.

The low LOS observed in the current trial may be a result of factors specific to the trial, unrelated to the trial, or, most likely, a combination of the two. It has been suggested that subjects enrolled in clinical trials may receive better overall medical management, which reduces morbidity and tends to eliminate differences that may have occurred in less rigorous settings.[19] Standardization of perioperative care and the resulting reduction in variation of care has been shown to improve outcome and reduce LOS.[20] Factors specific to our trial include perioperative clinical care according to explicit and detailed protocol, aggressive heart rate and MAP control, and intensive medically directed postoperative analgesic regimens. These factors may have contributed to our overall low incidence of postoperative morbidity, which could translate into a LOS benefit. Factors unrelated to the trial include the pressures from hospital administrators, third-party payers, and government agencies to reduce use of medical resources. We did find that patients enrolled during the latter 24 months of the trial had a small but statistically significant reduction in LOS compared with those enrolled during the first 24 months of the trial. However, this reduction in LOS was similar among the four treatment groups. Postoperative surgical management is another factor that obviously influences LOS. To address this, we prospectively established goals regarding nasogastric tube removal, initiation and advancement of feeding, ambulation, and hospital discharge (see Methods). Stratification of patients by surgeon also helped to ensure that systematic differences in postoperative care and hospital discharge did not confound the comparisons among and between treatment groups.

Not surprisingly, LOS is increased by postoperative complications.[21] LOS after major elective surgery has been associated with preoperative, intraoperative, and postoperative factors, with intraoperative management and postoperative adverse events being the factors that generate the highest risks for prolonged LOS.[22] Given the similar baseline clinical characteristics between treatment groups, our perioperative clinical care according to protocol, frequent acute pain service visits, and the similar overall postoperative complication rate, it is not surprising that we were not able to demonstrate a difference in LOS based on anesthetic or analgesic technique. Direct medical costs were also similar among the four treatment groups. LOS and postoperative complications are major factors contributing to costs after operative procedures. Given our similar LOS and complications rates between treatment groups, it is not surprising direct medical costs were also similar.

Limitations

An important limitation of this trial is that generalization of the conclusions, beyond the very select patient population studied and the very specific anesthetic and analgesic regimens used, may not be possible. Therefore, one cannot exclude the possibility that a similar trial in patients undergoing a different operative procedure may have revealed a LOS benefit attributable to the anesthetic or analgesic technique. Likewise, one cannot exclude the possibility that different anesthetic or analgesic regimens (different pharmacologic agents or dosages) may have resulted in a LOS benefit. The results of this trial do not exclude the possibility that some patients may have benefited from their treatment assignment, whereas others may have been adversely affected. Differentiation of those who benefited from those adversely affected is only possible if all potentially relevant determinants of outcome are known. In addition, as with most clinical trials, the results of this investigation are limited in time, and extrapolation of the results to a future time may be difficult.

Proposed benefits of regional anesthesia and analgesia include earlier ambulation and earlier return of bowel function.[23–25] No evidence for these benefits is seen in our results. Possible reasons for these negative findings include the lack of sufficiently aggressive feeding and ambulation protocols, which may reveal such benefits. It may also be argued that our regional analgesic regimen did not fully exploit the full potential of this modality.

For example, more concentrated solutions may confer more intense analgesia, although not without a greater incidence of side effects (hypotension and motor block).[26]

Patient recruitment was terminated because a conditional power analysis indicated a 0.6% chance of detecting a statistically significant difference in LOS among the four treatment groups if the trial was continued to the planned recruitment of 204 subjects. Ethical considerations associated with insertion of an unused epidural catheter (in 25% of patients), as well as the masked anesthetic and analgesic regimens, played a significant role in the decision of the monitoring committee to terminate patient recruitment. Using our factorial study design (two treatment groups), a two-sided type I error protection of 0.05, and the observed sample size (160 patients) and actual loss resulting from deaths (nine patients), our trial had a power of 0.99 and 0.79 to detect a 1.5-day (17% reduction) and 1.0-day (11% reduction) difference in LOS between groups, respectively. Therefore, although patient recruitment was terminated early, the trial remains appropriately powered for the hypothesized effect.

What are the implications of this study for future efforts to improve patient outcome with the use of regional anesthetic and analgesic techniques? The results of this trial suggest that future studies evaluating the potential benefits of regional anesthetic and analgesic techniques should use a multimodal approach with aggressive postoperative rehabilitation. In addition, such studies should focus on patient-meaningful and resource use outcomes, rather than the occurrence of rare or intermediate events with an unknown relation to true health outcomes. Given the difficulty of proving efficacy relating to rare adverse outcomes and of evaluating the role of one factor among many in the perioperative period, our inability to document the superiority of epidural anesthesia and analgesia should not significantly detract from their clinical use in other procedures and other patient populations, nor should it impede further clinical research to establish a relation between anesthetic and analgesic techniques and important health outcomes. Indeed, progress in the evolution of multimodal postoperative rehabilitation may eventually establish regional anesthesia and analgesia techniques as critical to the process.[27]

In conclusion, this double-masked randomized trial in patients undergoing abdominal aortic surgery was conducted to establish a relation between LOS and anesthetic or analgesic technique. The major finding of this investigation is that in patients undergoing surgery of the abdominal aorta, thoracic epidural anesthesia combined with a light GA and followed by either IVPCA or EPCA offers no major advantage or disadvantage when compared with GA alone followed by either IVPCA or EPCA.

The authors thank The Johns Hopkins Hospital anesthesiology and surgical residents, the attending, resident, and nursing staff of the Surgical Intensive Care Unit, and the attending, resident, and nursing staff of the Anesthesiology Acute Pain Service for patient management in compliance with our treatment protocols; Thomas A. Traill, M.D. (Professor, Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD), Peter B. Terry, M.D. (Professor, Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD), Henry A. Pitt, M.D. (Professor, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI), and Daniel P. Nyhan, M.D. (Associate Professor, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD), for service on the clinical monitoring committee; and Lee A. Fleisher, M.D. (Associate Professor, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD), for his expertise and contribution in reviewing the Holter tape recordings.

References

1. Pearson SD, Goulart-Fisher D, Lee TH: Critical pathways as a strategy for improving care: Problems and potential. Ann Intern Med 1995; 123:941–8

2. Bennett-Guerrero E, Welsby I, Dunn TJ, Young LR, Wahl TA, Diers TL, Phillips-Bute BG, Newman MF, Mythen MG: The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery. Anesth Analg 1999; 89:514–9

3. Kazmers A, Jacobs L, Perkins A: The impact of complications after vascular surgery in Veterans Affairs Medical Centers. J Surg Res 1997; 67:62–6

4. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T: Epidural anesthesia and analgesia in high-risk surgical patients. ANESTHESIOLOGY 1987; 66:729–36

5. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991; 73:696–704

6. Baron J, Bertrand M, Barre E, Godet G, Mundler O, Coriat P, Viars P: Combined epidural and general anesthesia *versus* general anesthesia for abdominal aortic surgery. ANESTHESIOLOGY 1991; 75:611–8

7. Bode RH, Lewis KP, Zarich SW, Pierce ET, Roberts M, Kowalchuk GJ, Satwicz PR, Gibbons GW, Hunter JA, Espanola CC, Nesto RW: Cardiac outcome after peripheral vascular surgery. ANESTHESIOLOGY 1996; 84:3–13

8. Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DCH, DeMajo WC, Walker PM, Johnston KW, Sandler AN: Epidural bupivacaine-morphine analgesia *versus* patient-controlled analgesia following abdominal aortic surgery. ANESTHESIOLOGY 1998; 89:585–93

9. Davies MJ, Silbert BS, Monney PJ, Dysart RH, Meads AC: Combined epidural and general anaesthesia versus general anaesthesia for abdominal aortic surgery: A prospective randomized trial. Anaesth Intens Care 1993; 21:790–4

10. Garnett RL, MacIntyre A, Lindsay P, Barber GG, Cole CW, Hajjar G, McPhail NV, Ruddy TD, Stark R, Boisvert D: Perioperative ischaemia in aortic surgery: Combined epidural/general anaesthesia and epidural analgesia vs general anaesthesia and iv analgesia. Can J Anaesth 1996; 43:769–77

11. Christopherson R, Beattie C, Frank SM, Norris EJ, Meinert CL, Gottlieb SO, Yates H, Rock P, Parker SD, Perler BA, Williams GM, The Perioperative Ischemia Randomized Anesthesia Trial Study Group: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. ANESTHESIOLOGY 1993; 79:422–34

12. Bois S, Couture P, Boudreault D, Lacombe P, Fugere F, Girard D, Nadeau N: Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative ischemia after aortic surgery. Anesth Analg 1997; 85: 1233–9

13. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies: A classification system. Circulation 1960; 21: 1160–75

14. Lave JR, Pashos CL, Anderson GF, Brailer D, Bubolz T, Conrad D, Freund DA, Fox SH, Keeler E, Lipscomb J: Costing medical care: Using Medicare administrative data. Med Care 1994; 32:JS77–89

15. Hoaglin DC, Mosteller F, Tukey JW: Understanding Robust and Exploratory Data Analysis. New York, Wiley, 1983, pp 40–1

16. Walraven C, Mahon JL, Moher D, Bohm C, Laupacis A: Surveying physicians to determine the minimal important difference: Implications for sample-size calculations. J Clin Epidemiol 1999; 52:717–23

17. Dardik A, Lin JW, Gordon TA, Williams GM, Perler BA: Results of elective abdominal aortic aneurysm repair in the 1990s: A population-based analysis of 2335 cases. J Vasc Surg 1999; 30:985–95

18. Lawrence PF, Gazak C, Bhirangi L, Jones B, Bhirangi K, Oderich G, Treiman G: The epidemiology of surgically repaired aneurysms in the United States. J Vasc Surg 1999; 30:632–40

19. Beattie C, Roizen MF, Downing JW: Cardiac outcomes after regional or general anesthesia: Do we know the question? ANESTHESIOLOGY 1996; 85:1207–9

20. Bradshaw BG, Liu SS, Thirlby RC: Standardized perioperative care protocols and reduced length of stay after colon surgery. J Am Coll Surg 1998; 186:501–6

21. McAleese P, Odling-Smee W: The effect of complications on length of stay. Ann Surg 1994; 220:740–4

22. Collins TC, Daley J, Henderson WH, Khuri SF: Risk factors for prolonged length of stay after major elective surgery. Ann Surg 1999; 230:251–9
23. de Leon-Casasola O, Karabella D, Lema M: Bowel function recovery after radical hysterectomies: Thoracic epidural bupivacaine-morphine versus intravenous patient-controlled analgesia with morphine: A pilot study. J Clin Anesth 1996; 8:87–92
24. Liu S, Carpenter R, Mackey D, Thirlby R, Rupp S, Shine T, Metzger P, Fulmer J, Smith S: Effects of perioperative analgesic technique on rate of recovery after colon surgery. ANESTHESIOLOGY 1995; 83:757–65
25. Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain J: Postoperative pulmonary complications: Epidural analgesia using bupivacaine and opioids versus parenteral opioids. ANESTHESIOLOGY 1993; 78:666–76
26. Liu S, Angel JM, Owens BD, Carpenter RL, Isabel L: Effects of epidural bupivacaine after thoracotomy. Reg Anesth 1995; 20:303–10
27. Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H: A clinical pathway to accelerate recovery after colonic resection. Ann Surg 2000; 232:51–7

Appendix 1: Masked Epidural and Intravenous Boluses and Continuous Infusions

General Anesthesia

1. Intravenous bolus: fentanyl equivalent to 10 μg/kg (body weight).
2. Intravenous continuous infusion: fentanyl at a rate equivalent to 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$.
3. Epidural bolus: normal saline (6 or 8 ml).
4. Epidural continuous infusion: normal saline at 6 ml/h.

Regional Supplemented General Anesthesia

1. Epidural bolus: 6 ml (left flank incision) or 8 ml (midline incision) of 0.5% bupivacaine with 50 μg fentanyl.
2. Epidural continuous infusion: 0.125% bupivacaine with 5 μg/ml fentanyl at 6 ml/h.
3. Intravenous bolus: normal saline.
4. Intravenous continuous infusion: normal saline.

Appendix 2: Management of the Masked Intraoperative Epidural and Intravenous Continuous Infusions

1. Deviations of heart rate or MAP outside of the preset limits were treated first by adjustment of inhalational agent or fluid or blood infusion, and then by adjustment of the masked epidural and intravenous infusions as detailed below.
2. Patients requiring more than 0.8% end-tidal enflurane for more than 5 min to maintain heart rate and MAP limits received:
   (a) a 5-ml bolus of the masked epidural infusion and a rate increase of 2 ml/h; and
   (b) a 2-μg/kg bolus of the masked intravenous infusion and a rate increase equivalent to 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$.
3. Patients requiring less than 0.2% end-tidal enflurane for more than 5 min to maintain heart rate and MAP limits received:
   (a) a decrease in the masked epidural infusion rate of 2 ml/h; and
   (b) a decrease in the masked intravenous infusion rate equivalent to 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$.
4. Appropriate pharmacologic (esmolol, labetalol, phenylephrine, ephedrine, sodium nitroprusside, and nitroglycerin) manipulation of heart rate and MAP was used when the above measures proved inadequate and while waiting for anesthetic adjustments to take effect.

Appendix 3: Intraoperative Fluid, Blood, and Urine Output Management

1. Fluids were managed to maintain a pulmonary capillary wedge pressure between 2 mmHg greater or less than a stable baseline pulmonary capillary wedge pressure obtained just before skin incision.
2. Appropriate amounts of fluids for maintenance and replacement of blood loss were calculated and administered.
3. Sodium nitroprusside and nitroglycerin were administered during the period of aortic cross-clamping, as necessary, to maintain pulmonary capillary wedge pressure and mean blood pressure within the predetermined limits.
4. All patients received 12.5 g mannitol intravenously approximately 30 min before aortic cross-clamping.
5. Patients requiring aortic cross-clamping above the renal arteries and those with preoperative renal insufficiency (creatinine concentration $\geq$ 1.5 mg/dl) received 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine *via* continuous infusion before and during aortic cross-clamping.
6. Urine output was maintained at greater than 2 ml $\cdot kg^{-1} \cdot h^{-1}$ before aortic cross-clamping and again after removal. Furosemide (5–20 mg) was administered if urine output was not maintained with fluids and mannitol.
7. Hemoglobin was maintained at greater than or equal to 10 g/dl using autologous, scavenged (Cellsaver; Haemonetics, Braintree, MA), or allogeneic transfusions. Intraoperative hemoglobin was monitored with a β-hemoglobin analyzer (Hemocue, Angelholm, Sweden).

Appendix 4: Masked Postoperative Patient-controlled Analgesia Management

Masked Epidural Bolus

1. Patients who received RSGA intraoperatively received 6 ml of 0.0625% bupivacaine with 50 μg fentanyl epidurally if randomized to EPCA postoperatively, or 6 ml of normal saline epidurally if randomized to IVPCA postoperatively.
2. Patients who received GA intraoperatively received 6 ml of 0.25% bupivacaine with 50 μg fentanyl epidurally if randomized to EPCA postoperatively, or 6 ml of normal saline if randomized to IVPCA postoperatively.

Masked Postoperative Patient-controlled Analgesia

1. Patients randomized to EPCA received 0.0625% bupivacaine with 5 μg/ml fentanyl *via* the epidural pump and normal saline *via* the intravenous pump.
2. Patients randomized to IVPCA received 10 μg/ml fentanyl *via* the intravenous pump and normal saline *via* the epidural pump.
3. All PCA adjustments were controlled by protocol (see below) and required simultaneous pump programming (*i.e.*, both epidural and intravenous pumps were always programmed exactly the same so that they delivered the same basal rates with the same delay, dose, and limit).
4. No additional opioids or adjunctive analgesics were permitted while the masked postoperative PCA regimen was active.
5. Patients who experienced an epidural catheter malfunction that could not be corrected received unmasked intravenous morphine PCA as necessary. Patients that required unmasking of their postoperative analgesic regimens also received unmasked intravenous PCA.

Masked Patient-controlled Analgesia Protocol

1. Initial dose regimen: dose = 4 ml; delay = 8 min; basal rate = 8 ml/h.
2. Dosage increase protocol.
   (a) For first complaint of pain (after initiation):
      (1) increase dose to 6 ml (if self-dosing $\geq$ 3/h);
      (2) administer 6-ml bolus;
      (3) no change in delay or basal rate.

(b) For all subsequent complaints of pain:
(1) change only if self-dosing average is greater than or equal to 3/h (during previous 4 h);
(2) increase dose by 2 ml;
(3) administer bolus equal to new dose;
(4) no change in delay or basal rate.

3. Dosage decrease protocol.
(a) No decrease should be made on the day or evening of surgery unless the patient is unduly sedated (not responding to simple commands).
(b) Beginning on postoperative day 1 at 7 AM:
(1) if self-dosing less than 1/h during previous 4 h, decrease basal rate to 4 ml/h;
(2) if subsequent self-dosing less than or equal to 1/h during 4 h or more, decrease dose by 1 ml;
(3) if subsequent self-dosing less than or equal to 1/h during 4 h or more, decrease basal rate by 1 ml/h;
(4) if subsequent self-dosing less than or equal to 1/h during 4 h or more, alternatively repeat (2) and (3);
(5) minimal dose = 1 ml, minimal basal rate = 0 ml/h.
(c) If hypotension develops, pumps will be turned off and the Acute Pain Service attending notified. On adequate restoration of blood pressure, resume basal rate at one half the previous rate and resume previous dose and delay.

4. Dosage increase protocol after previous decrease. Follow dosage increase protocol.
5. Dosage decrease protocol after previous increase. Follow dosage decrease protocol.
6. Treatment for pruritus.
(a) Naloxone 1 mg in 1,000 ml normal saline at 20 ml/h as needed.
(b) If pruritus continues, add diphenhydramine 25 mg intravenously every 4 h as needed.
7. Treatment for nausea and/or vomiting.
(a) Metoclopramide 20 mg intravenously every 4 h as needed.
(b) If nausea or vomiting continues after second dosage of metoclopramide, add naloxone 1 mg in 1,000 ml normal saline at 20 ml/h.
8. Initiation of Activity.
(a) Check motor strength in lower extremities and orthostatic blood pressure before first time out of bed.
(b) Check motor strength every 4 h while awake.
(c) Check orthostatic blood pressure first time out of bed daily.
(d) Check heart rate and blood pressure every 2 hours while out of bed.
9. Transition to oral analgesics.
(a) Transition initiated by Acute Pain Service attending physician only.
(b) Patient must be tolerating clear liquids for more than 24 h.