

Clinical Outcomes after Lower Extremity Revascularization: A Comparison of Epidural and General Anesthesia

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ABSTRACT

Objective: This study tests the hypothesis that epidural anesthesia during, and epidural analgesia after, lower extremity vascular surgery decreases the incidence of postoperative morbidity compared with general anesthesia.

Method: Using a prospective, randomized, non-blinded clinical trial design, 82 patients scheduled for lower extremity revascularization surgery were randomized to either epidural anesthesia and postoperative analgesia or general anesthesia and systemic opioid analgesia during and after surgery. Measurements were made of preoperative patient demographic data, intraoperative anesthetic management, and intra- and postoperative clinical outcomes including major organ system morbidity and vas-

cular graft function. Patients in the two groups were similar before surgery.

Results: There were no significant differences in major organ system morbidity after surgery or in hospital length of stay. Patients randomized to the epidural group had a decreased incidence of early vascular graft failure at 7 days after surgery, a difference that was no longer significant by 30 days after surgery.

Conclusions: Epidural anesthesia and analgesia decreased the incidence of early lower extremity vascular graft failure within 7 days of surgery. This favorable effect on graft function was no longer present 30 days after surgery.

INTRODUCTION

Patients who undergo peripheral vascular surgery are at risk for surgery-specific complications such as vascular graft failure. As a consequence of pre-existing co-morbidities, vascular surgical patients

also commonly present with minimal organ reserves, leading to an additional risk of non-surgical site complications, especially cardiopulmonary complications.¹⁻⁵ Over the past two decades, substantial clinical evidence has been generated and published regarding the potential influence of perioperative anesthetic management on many of the clinical outcomes that follow surgery. These studies range from investigations that measured the impact of anesthetic care on immediate postoperative events such as pain and nausea,⁶ to the occurrence of intermediate outcomes such as respiratory insufficiency,⁷ to measurements of the potential impact of perioperative anesthetic management on long-term survival.^{8,9} The most convincing data to suggest an effect of perioperative anesthetic management on clinical outcomes after surgery have been reported for patients who, like vascular surgical patients, are known to experience a relatively high proportion of adverse events after surgery.⁹⁻¹¹

Many clinical trials in anesthesia have compared the clinical effects and outcomes of regional anesthesia (with or without postoperative regional analgesia) to those of general anesthesia and systemic postoperative analgesia. The most recent studies have been conducted in an evolving health care environment where rapid changes in practice patterns have made it difficult to isolate an independent anesthetic effect on surgical outcomes, especially when a study is conducted over a period of several years.¹² Despite the difficulty of conducting clinical studies in a changing health care environment, there are many physiologic effects and theoretical benefits of regional anesthesia that could be of particular benefit to the vascular surgical patient. The potential benefits of regional techniques include control of hemodynamic responses to surgery with improved cardiovascular perform-

ance,^{13,14} minimization of hormonal responses to surgery (especially hypercoagulability),^{15,16} increased lower extremity blood flow,^{17,18} and better pain control with minimization of postoperative sedation.^{6,8,11,19} Recent retrospective reviews of large vascular surgical databases continue to suggest an outcome benefit when regional anesthesia is compared with general anesthesia.^{20,21}

Despite this, there are few randomized trials of the two types of anesthesia in patients scheduled for infrainguinal bypass surgery. To better define the impact of regional techniques on operative outcomes in vascular surgical patients, we conducted a clinical trial to test the hypothesis that regional anesthesia and analgesia, when compared with general anesthesia and systemic opioid analgesia, would decrease the incidence of both surgery-specific and non-surgery specific complications following lower extremity revascularization.

MATERIALS AND METHODS

This study was approved by the Dartmouth College Committee for the Protection of Human Subjects (Institutional Review Board) and written informed consent was obtained from all study participants.

Patient Population

Patients were considered candidates for inclusion in the study if they were scheduled to undergo a femoral-popliteal or femoral-distal revascularization procedure, if they were 50 years of age or older, and if they consented to participate. Exclusion criteria included patients who had previously had a vascular surgical procedure on the same leg or who had any contraindication to the use of epidural anesthesia (pre-existing neurologic deficit, infection at catheter insertion site, coagulopathy). Patients who met the above criteria were considered

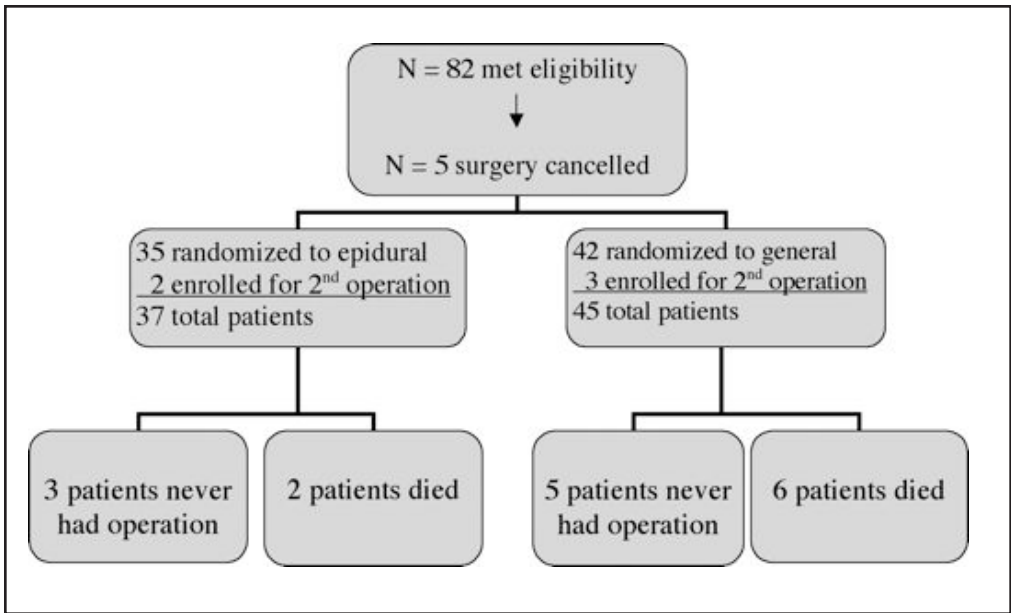


Figure 1. Study enrollment chart.

candidates for study enrollment and, if they provided informed consent, were randomized to receive either epidural anesthesia/analgesia or general anesthesia and systemic opioid analgesia.

Intraoperative Anesthesia

Patients who were randomized to the general anesthesia (GA) group received benzodiazepine premedication followed by anesthesia induction with fentanyl, 2-5 mg/kg, and thiopental, 3-5 mg/kg. Muscle relaxation was used as required to facilitate endotracheal intubation and surgical anesthesia. Anesthesia was maintained with nitrous oxide, further fentanyl supplementation, and a potent inhalational agent as determined by the anesthesiologist caring for the patient. Following surgery, patients in the GA group received intravenous (IV) opiate analgesia until they were able to begin oral intake of pain medications. Patients randomized to the epidural anesthesia (EA) group were given small IV doses of a benzodiazepine immediately prior

to the insertion of an epidural catheter in a mid-lumbar interspace using a loss-of-resistance technique for identification of the epidural space. Epidural catheters were placed immediately prior to surgery in the operating room. Epidural anesthesia was induced with incremental doses of 1.5% lidocaine with epinephrine 1:200,000 to establish an upper sensory level at approximately the sixth thoracic dermatome. During surgery, further doses of local anesthetic in the epidural catheter and intermittent IV doses of a benzodiazepine and/or fentanyl were used to maintain patient sedation and comfort. Postoperative analgesia was initiated after surgery using a continuous infusion of 0.125% bupivacaine with 3 mg/mL of fentanyl at a rate of 6-10 mL/h. In some cases, a decision was made at the end of surgery to remove the epidural catheter, in which case the patients were given 10 mL of 0.25% bupivacaine upon arrival in the recovery room after surgery, and the epidural catheter was then removed.

Table 1. Preoperative Patient Characteristics of the Treatment Groups*

GROUP	General anesthesia (GA)	Epidural anesthesia (EA)
Number in group	45	37
Age	67 (10)	69 (10)
Male (%)	62	62
Angina history (%)	31	27
Previous MI (%)	33	22
Previous CHF (%)	24	19
Previous CABG (%)	7	3
Hypertensive (%)	64	57
Diabetes (%)	62	59
COPD (%)	20	19
Currently smoking (%)	53	51
Creatinine (mg/dL)	1.6 (1.1)	1.4 (1.6)

*There were no statistically significant differences between groups for any measurement. Numbers in parentheses are \pm [PLUS OR MINUS SYMBOL]SD. MI=myocardial infarction; CHF=congestive heart failure; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease

Non-anesthetic Management

Other than the specific anesthetic and analgesic treatments, other aspects of perioperative patient management were not dictated by study protocol.

Interventions such as fluid management, red blood cell transfusions, hemodynamic monitoring and therapy, and surgical management decisions were not affected by study participation. Postoperative thrombosis prophylaxis was not routinely prescribed.

Measurements

Patients were followed for 1 year or until death. The following measurements were recorded:

1. Specific pre-operative patient demographics as presented in the Results section.
2. Surgical data including indications for surgery, length of surgery, blood loss, type of procedure, and graft failure within 1 year of surgery as evidenced by the need for a repeat procedure for limb or graft salvage

(embolectomy, graft revision, angioplasty) or graft failure with amputation (above the ankle). Graft failure was assessed on postoperative days 7 and 30 and at 6 and 12 months after surgery.

3. Myocardial ischemia was assessed by continuous Holter monitoring beginning on the morning of surgery and maintained for 36 hours. Bipolar lead CS5 and a modified lead II were recorded and analyzed. Ischemia was defined as ≥ 1.0 mm of flat or downsloping ST segment depression persisting for 60 milliseconds after the J-point and lasting for ≥ 1 minute. In the presence of ST depression at baseline, a further depression of 1.5 mm from baseline was required to meet the criteria for ischemia. ST elevation of ≥ 1.5 mm was also defined as ischemia.
4. The occurrence of organ-specific complications was assessed during hospitalization, including congestive heart failure as documented by clas-

Table 2. Operative Indications and Characterization of Conduit and Outflow Artery*

GROUP	General anesthesia (GA)	Epidural anesthesia (EA)
Indication (%)		
Claudication	13	11
Rest Pain	18	24
Tissue loss	69	65
Conduit (%)		
Ipsilateral saphenous	91	95
PTFE	9	5
Outflow artery (%)		
Above knee	4	8
Below knee	96	92

*There were no statistically significant differences between groups for any measurement.
PTFE=polytetrafluoroethylene (Gortex) graft

sis radiographic changes plus new rales on pulmonary auscultation or a pulmonary catheter wedge pressure greater than 20 mmHg and requiring treatment; unstable angina, defined as recurrent chest pain at rest with associated electrocardiographic (ECG) changes; myocardial infarction, defined as elevated creatine phosphokinase-MB (CPK-MB) in blood with new Q-waves on the ECG or persistent electrocardiographic abnormalities and a diagnosis corroborated by an independent cardiologist; respiratory failure, defined as either postoperative tracheal reintubation and/or mechanical ventilation for more than 24 hours after surgery; renal insufficiency, defined as a postoperative rise in creatinine of more than 1.5 mg/dL above baseline; a major infection, defined as either pneumonia (new infiltrate on chest x-ray with temperature greater than 38°C, elevated white blood cell count, and positive sputum culture) or sepsis (a positive blood culture with temperature >38°C or <35°C and antibiotic

treatment); or a surgical wound infection requiring antibiotic treatment.

Statistical Methods

During development of the study protocol, a retrospective chart review of recent peripheral vascular surgical procedures was used to determine the incidence of major complications in the projected population of patients who would be eligible for study enrollment. These data were combined with previously published data on the expected reduction in complication rates for a high-risk surgical population.²² Assuming that we would observe an equal reduction in the overall rate of complications, we planned to study 100 patients with 1:1 randomization to each of the two treatment groups. The study was terminated after enrolling a total of 82 patients for two reasons. First, a conditional analysis of the major morbidity we had observed after enrolling 82 patients suggested an extremely low likelihood that we would observe a clinical benefit at 100 patients. Using the original data on complication incidence

Table 3. Intraoperative Characteristics of Patients in the Two Treatment Groups*

GROUP	General anesthesia (GA)	Epidural anesthesia (EA)
Hemodynamics (%)†		
Decreased HR	3	0
Increased HR	10	15
Decreased BP	20	46*
Increased BP	22	8
Fluids (mL)		
Estimated blood loss	499 (373)	402 (293)
Crystalloid administered	3308 (1119)	2877 (1033)
Surgery duration (min)	298 (99)	295 (89)

*There were no statistically significant differences between groups for any measurement except as noted.
†Changes in heart rate or blood pressure requiring treatment with vasoactive agents.
HR=heart rate; BP=blood pressure;
Numbers in parentheses are ± SD.
*P=0.02

and relative reduction in events, a study size of 82 patients calculated an 80% power to detect a significant difference in the rate of postoperative complications at the 0.01 significance level (Fisher's exact test). Second, a rapid increase in the postoperative use of fractionated heparin products caused concern regarding the continued implementation of postoperative epidural catheter analgesia for the patients under study. For analysis of observed events in the 82 patients who completed the study, continuous variables were compared using analysis of variance, and ordinal data were compared using Fisher's exact test with a P -value <0.05 considered significant. Time-to-failure analysis was completed using Kaplan-Meier techniques to determine time to graft failure for the two groups,²³ with the log rank test used as a test of statistical significance.²⁴

RESULTS

Patient Groups

In total, 82 patients consented to participate in the study; surgery for 5 patients

was cancelled prior to randomization, leaving 77 randomized patients. During the course of the study, 2 patients who were originally randomized into the GA group and 3 patients originally randomized to the EA group underwent a second procedure on the contralateral leg and were automatically assigned to the opposite treatment group, returning the total number of study patients to 82 (Figure 1). Of the final 82 patients, 8 patients (5 in the GA group, 3 in the EA group) did not undergo an index operation (surgery cancelled [5]; aorto-bifemoral bypass, angioplasty, and embolectomy [1 each]). All 82 patients are included in the intent-to-treat analysis reported below (although exclusion of these 8 patients [analysis by actual treatment] does not alter the statistical results of the intent-to-treat analysis.) Two patients in the EA group received continuous spinal anesthesia instead of continuous epidural anesthesia; 1 patient in the EA group received a general anesthetic when regional anesthesia was unsuccessful; these 3 patients are included in the EA group for analysis by

Table 4. Incidence of Perioperative Morbidity during Initial Postoperative Hospitalization*

GROUP	General anesthesia (GA)	Epidural anesthesia (EA)
Death (%)	4	0
Cardiac event (%)†	16	11
Heart failure (%)	13	8
Unstable angina (%)	9	3
Myocardial infarction (%)	7	5
Myocardial ischemia‡ (%)	45	31
Respiratory failure (%)	7	0

*There were no statistically significant differences between groups for any measurement.
†Patients with one or more of the following: congestive heart failure, unstable angina, myocardial infarction, or cardiac death
‡One or more episodes of ischemia on Holter recording

intent-to-treat. Epidural catheters were removed on the day of surgery in 6 patients, on postoperative day (POD) 1 in 18 patients, on POD 2 in 6 patients, and on POD 3 in 1 patient; 3 patients did not have epidural catheters placed (2 spinal catheters [removed day of surgery] and 1 conversion to general anesthesia, as noted above).

Preoperative Measurements

The preoperative characteristics, comorbidities, and past medical histories of cardiopulmonary disease were not significantly different between the two patient groups (Table 1). The operative indications also were not significantly different between the two patient groups (Table 2).

Intraoperative Measurements

Intraoperative characteristics of the procedures in the two patient groups were equivalent, including a mean surgical duration that was virtually the same for both groups (Table 3). Patients in the EA group were more likely to be treated for decreased blood pressure ($P=0.02$), while patients in the GA group were treated more often for increased blood pressure (P =not signifi-

cant). Blood loss and intraoperative crystalloid administration were also not significantly different between groups. The conduit used (vein or graft) and the outflow artery were comparable between the two groups as well (Table 2).

Postoperative Measurements

Overall, the incidence of postoperative morbidity was less than expected, with no significant differences between the two groups (Table 4). There were two deaths during the initial hospitalization in the GA group and no deaths during the initial hospitalization in the EA group. Episodes of congestive heart failure, unstable angina, and myocardial infarction were not significantly different between groups, while 45% of patients in the GA group and 31% of patients in the EA group had one or more episodes of postoperative myocardial ischemia as detected on continuous ECG (Holter) monitoring during the first 24 postoperative hours (P =not significant). Episodes of respiratory failure were also not different between the two groups. Significantly more patients in the GA group (6 of 45) required a reoperation for limb or graft salvage within 7

Table 5. Incidence of Postoperative Vascular Graft Failure Analyzed by Intent-to-Treat and by Actual Treatment Received

Intent-to-treat				
GROUP	7 days	30 days	6 months	1 year
General	6/45	7/45	10/45	10/45
Epidural	0/37	2/37	8/37	9/37
<i>P</i> -value	0.02	0.16	NS	NS
Actual treatment				
GROUP	7 days	30 days	6 months	1 year
General	6/40	7/40	10/40	10/40
Epidural	0/34	2/34	8/34	9/34
<i>P</i> -value	0.03	0.18	NS	NS
NS=not statistically significant				

days of the index surgery (GA, 13%; EA, 0%), a difference that was statistically significant ($P=0.02$). As noted, this difference was also significant at 7 days when analyzed by actual treatment received (Table 5). At 30 days, there continued to be a trend of more graft failures in the GA group (GA, 16%; EA, 5%), but this trend was not significant ($P=0.16$). By 6 months the proportion of surviving patients with primarily patent grafts was similar for the two groups (Table 5, Figure 2).

DISCUSSION

The results of this clinical study are consistent with previous reports suggesting that patients who receive epidural anesthesia during lower extremity vascular bypass surgery may have better early vascular graft patency rates compared with patients who receive general anesthesia.^{4,5} A similar, large retrospective study also showed a difference in graft patency.²⁰ In contrast, Pierce et al conducted a follow-up chart review on a prospective study and found no impact of anesthetic technique on graft patency rates.²⁵ It is interesting to note, however, that the authors in the latter study

reported a mean time to graft failure in their general anesthesia group of 3.8 days compared with a mean time to failure in their epidural group of 11.3 days, consistent with our data showing an early benefit of regional anesthesia for graft patency. There are several mechanisms to explain how regional anesthesia may temporarily improve vascular graft patency in the postoperative period.

Regional anesthesia improves lower extremity graft blood flow via two potential mechanisms. Cousins et al showed many years ago that induction of epidural anesthesia improved blood flow by over 50% in a lower extremity bypass graft.¹⁷ In their study, patients had an epidural catheter inserted before lower extremity vascular surgery that was then performed under general anesthesia. The epidural catheters were not used until after the graft was completed, at which time blood flow through the graft was measured by a flow probe and then measured again after the injection of local anesthetic into the epidural catheter, which resulted in substantial increases in graft blood flow. Although the overall increase in blood flow may have been due to decreased lower

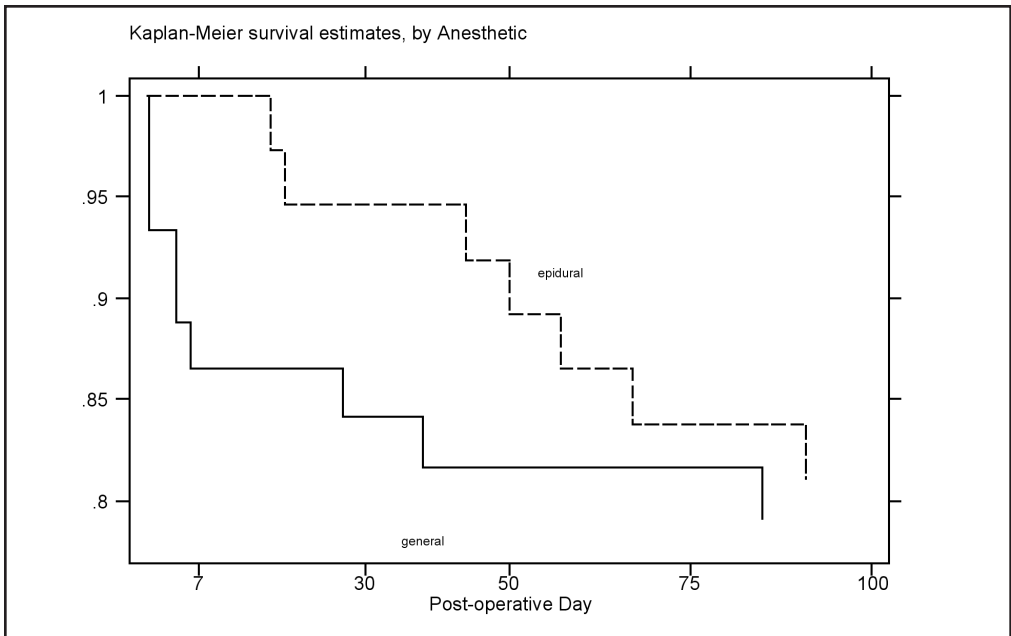


Figure 2. Kaplan-Meier curve graph showing time to graft failure after the primary operation. There were significantly more failures at 7 days after surgery in the general anesthesia (GA) group (solid line) compared with the epidural analgesia (EA) group (dashed line) ($P=0.02$). This difference was not significant at 30 days, 6 months, or at 1 year.

extremity sympathetic tone, this was not documented. A second mechanism by which regional anesthesia can improve lower extremity and vascular graft blood flow is by avoiding positive pressure ventilation. When epidural anesthesia is used alone without general anesthesia (as in the present study), patients avoid positive pressure ventilation, which is well-documented to decrease cardiac output and lower extremity blood flow.^{26,27} Comparisons between epidural anesthesia and general anesthesia during hip and prostate surgery have also shown a significantly greater lower extremity venous blood return with fewer thromboembolic events after epidural anesthesia, presumably due to avoidance of positive pressure ventilation and, perhaps, to redistribution of blood flow.^{28,29} Since graft blood flow is a strong predictor of long-term graft patency,³⁰ any intervention that acts to improve graft blood flow may be expect-

ed to improve graft patency rates. In fact, when cardiac output is aggressively managed with invasive hemodynamic monitoring to optimize fluid and vasoactive drug use, graft patency rates after lower extremity revascularization are very high.^{25,31}

Epidural anesthesia has also been shown to attenuate some measures of hypercoagulability after major surgery, including lower extremity revascularization. Vascular surgery patients as a group demonstrate increased coagulability compared with normal controls.³² In the early postoperative period, blood coagulability increases further, making these patients susceptible to thrombotic events.^{5,32,33} Tuman showed that epidural anesthesia attenuated the postoperative increase in platelet aggregation in a group of vascular surgical patients. This effect was associated with fewer episodes of arterial thrombosis after major vascular surgery.⁵ Similarly,

Rosenfeld¹⁵ reported that epidural anesthesia for lower extremity revascularization was associated with better fibrinolytic activity after lower extremity vascular surgery. These same authors also reported fewer episodes of early lower extremity vascular graft failure in patients receiving intraoperative epidural anesthesia and postoperative epidural opioid analgesia compared with patients who received general anesthesia.⁴ The differences, however, also disappeared within 30 days of surgery. Finally, Park et al reported fewer episodes of cerebral thrombosis after major vascular surgery when patients received intraoperative epidural anesthesia to supplement general anesthesia.¹¹ These data, taken together, provide evidence that (1) epidural anesthesia during major vascular surgery attenuates the usual increase in postoperative hypercoagulability, (2) this effect may have short-term benefits in vascular grafts with tenuous patency, and (3) the effects are not durable.

Other possible effects of regional anesthesia on vascular graft patency include attenuation of postoperative pain with the accompanying sympathetic response and the use of volume loading that often accompanies neuraxial blockade, leading to rheological changes in blood. We did not maintain postoperative epidural analgesia beyond the operative day in all patients and so, although it is possible that regional analgesia after vascular surgery may have affected sympathetically induced changes in lower extremity graft flow and patency, the data presented here do not allow any conclusions to be drawn about effects of postoperative regional analgesia. In addition, none of the 6 patients who had their epidural catheters removed on the operative day experienced postoperative thrombotic complications. Since patients in the EA group actually received less intraoperative crystalloid, on average, than patients in the GA group, it seems

unlikely that IV fluid-induced changes in blood rheology affected graft patency rates.

The overall incidence of major organ system morbidity was less than expected at the time that this study was initiated. Reports in the literature and our own experience with vascular surgical patients, including a retrospective chart review, had suggested complication rates in the range of 40-50%, which was clearly much higher than the rates we observed in this study. The difference is probably due to differences in patient populations and to ongoing clinical improvement efforts designed to decrease postoperative complications. With a relatively low incidence of major morbidity, this study was underpowered to detect any significant treatment effect on postoperative morbidity, if one existed, as a consequence of the use of epidural anesthesia and analgesia. Some minor clinical differences such as the frequency of treatments for increased or decreased blood pressure were observed but, appropriately managed according to best clinical care, these do not represent significant clinical events.³¹

Overall, the results presented here are consistent with reports from other investigators, who show that regional anesthesia during lower extremity revascularization may improve early vascular graft patency rates by a variety of potential mechanisms. The clinical significance of this effect is minimized by the fact that overall morbidity and long-term graft patency rates may be unaffected. It is as yet unknown whether or not the use of newer, and more potent, antithrombotic agents can sustain (or obviate) the favorable impact of regional anesthesia on early graft patency rates.

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