Premedication with Oral and Transdermal Clonidine Provides Safe and Efficacious Postoperative Sympatholysis

John E. Ellis, MD*, Greet Drijvers, MD*, Steven Pedlow, MS†, Scott P. Laff, MD*, Matthew J. Sorrentino, MD‡, Joseph F. Foss, MD*, Manish Shah, BS*, J. R. Busse, MD*, Srinivas Mantha, MD*, James F. McKinsey, MD§, Joachim Osinski, MS*, Ronald A. Thisted, PhD*†, Michael F. Roizen, MD*

Departments of *Anesthesia and Critical Care, †Statistics, ‡Medicine (Section of Cardiology), and §Surgery, The University of Chicago, Chicago, Illinois

We studied 61 patients undergoing elective major noncardiac surgery in a randomized, double-blind, placebo-control clinical trial to test the hypothesis that the addition of clonidine to a standardized general anesthetic could safely provide postoperative sympatholysis for patients with known or suspected coronary artery disease. Patients were allocated randomly to receive either placebo ($n = 31$) or clonidine ($n = 30$). The treatment group received premedication with a transdermal clonidine system (0.2 mg/d) the night prior to surgery, which was left in place for 72 h, and 0.3 mg oral clonidine 60–90 min before surgery. Clonidine reduced enflurane requirements, intraoperative tachycardia, and myocardial ischemia (1/28 clonidine patients vs 5/24 placebo, $P = 0.05$). However, clonidine decreased heart rates only during the first five postoperative hours; the incidence of postoperative myocardial ischemia (6/28 clonidine vs 5/26 placebo) did not differ between the two groups. Patients who experienced postoperative myocardial ischemia tended to have higher heart rates after surgery. Clonidine significantly reduced the plasma levels of epinephrine ($P = 0.009$) and norepinephrine ($P = 0.026$) measured on the first postoperative morning. There were no differences in the need for intravenous fluid therapy or antihypertensive therapy after surgery. The number of hours spent in an intensive care setting and the number of days spent in hospital were not different between the two groups. These results suggest that larger doses of clonidine should be investigated for their ability to decrease postoperative tachycardia and myocardial ischemia.

(Anesth Analg 1994;79:1133–40)

Substantial morbidity, mortality, and costs are associated with coronary artery disease (CAD) in elderly surgical patients, particularly in those who have vascular surgery (1). Electrocardiogram (ECG) monitoring has been used to document that patients with CAD are more likely to manifest myocardial ischemia after surgery rather than before surgery (2). Clonidine is an α_2-adrenergic agonist with the potential to improve outcome in high-risk patients undergoing noncardiac surgery (3,4). Unreported in the previously noted studies, however, is the incidence of later hemodynamic abnormalities, myocardial ischemia, or clinical complications. Sympatholytic therapies should be evaluated beyond the first few postoperative hours because the adrenergic response to surgery persists for at least several days (5) and increases postoperative congestive heart failure, renal dysfunction (6), nitrogen loss (7), and immune suppression (8).

The combination of oral and topical clonidine represents an inexpensive sympatholytic therapy ($12.50/transdermal system, $4.25/0.3-mg oral dose) with the potential to reduce the incidence of perioperative myocardial ischemia by reducing the hypertension and tachycardia that accompany vascular surgery. Transdermal application of clonidine allows continuous sympatholytic therapy in surgical patients who may not be able to take oral medications and, consequently, might help reduce the need for intravenous infusions of potent antihypertensive medications. We hypothesized that the addition of

This work was supported by an Anesthesiology Young Investigator Award from the Foundation for Anesthesia Education and Research.

Presented in part at the International Anesthesia Research Society, 1992, San Diego, CA.

Accepted for publication August 19, 1994.

Address correspondence and reprint requests to John E. Ellis, MD, Department of Anesthesia and Critical Care, Box MC 4028, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637.

0003-2999/94/$5.00

clonidine to a general anesthetic, consisting of low doses of sufentanil with enflurane in nitrous oxide, would reduce anesthetic requirements, reduce the postoperative adrenergic response, and decrease the incidence of perioperative myocardial ischemia in patients with risk factors for CAD.

Methods

After Institutional Review Board approval and written patient consent, 61 patients undergoing elective, major, noncardiac surgery were enrolled between November 14, 1990, and May 1, 1992. We anticipated that the patients would spend the evening after surgery in an intensive care setting. These patients had known CAD or at least two of the following clinical risk factors for CAD: peripheral vascular disease, age > 70 yr, a history of cigarette smoking, hypertension, diabetes mellitus, or an abnormal ECG. Exclusion criteria included chronic α-methyl dopa or clonidine therapy, serum creatinine > 3.0 mg/dL, planned carotid endarterectomy surgery, planned thoracic aortic aneurysm surgery, pulse < 50 bpm, or PR interval > 0.24 s.

Enrolled patients were randomly allocated to receive either placebo (n = 31) or clonidine (n = 30). During the night before surgery, the treatment group received a transdermal system which released 0.2 mg/day of clonidine and 60–90 min before surgery received a 0.3 mg oral loading dose of clonidine. The control group received placebo patches and pills. Treatment allocations without stratification were made using computer-generated random numbers which were recorded in sequentially numbered, sealed envelopes by the study statistician. These envelopes were held by the research pharmacist who opened the next envelope in sequence when a patient enrolled in the study. Patients, anesthesiologists, surgeons, and postanesthesia care unit and intensive care unit (ICU) personnel were blinded as to treatment throughout the perioperative period. Blood levels of clonidine were determined and held separately from other study records and were not available to the investigators during the study. An unblinded Safety and Data Monitoring Committee consisting of a statistician and an anesthesiologist reviewed all cases for adverse experiences possibly related to treatment. The clonidine skin patch was removed 72 h after application, unless hypotension (systolic blood pressure < 90 mm Hg, unresponsive to fluid challenge) or a major complication (myocardial infarction or cardiac arrest) ensued; in such cases, the patch, whether active or placebo, was immediately removed.

Patients were premedicated with morphine, 0.1 mg/kg intramuscularly, and any chronic cardiac and antihypertensive medications 60 min before surgery. Midazolam 1–2 mg intravenously (IV) was administered to facilitate arterial line placement. General anesthesia was induced with sufentanil (0.5 μg/kg), thiamylal (1–5 mg/kg total in 50-mg increments), and vecuronium (0.1 mg/kg) IV. After endotracheal intubation, anesthesia was maintained with enflurane (measured by infrared absorption spectroscopy) in 50% nitrous oxide. If the inspired concentration of enflurane reached 2% and hemodynamics were not within 20% of mean ward baseline heart rate and systolic blood pressure, sufentanil 5–10 μg IV was given. In addition, sufentanil 5–10 μg was given at the beginning of wound closure. Vecuronium was administered to maintain muscle relaxation. The use of central venous catheters, pulmonary artery catheters, and colloid infusions was not standardized; rather, they were used at the discretion of the attending anesthesiologist. All IV fluids were warmed, fresh gas flows of < 2 L/min were used, and a Humid-vent® (Gibeck Respiration, Upplands Väsby, Sweden) heat and moisture exchanger was attached to the endotracheal tube. When possible, we attempted to extubate the patients' tracheas after skin closure in the operating room.

Intraoperative invasive blood pressures and expired gas concentrations were downloaded into a personal computer every 60 s. Hemodynamic instability was defined as a period > 5 min during which hemodynamics were out of the following "preset boundaries": tachycardia = heart rate > 100 bpm; bradycardia = heart rate < 60 bpm; hypertension = systolic blood pressure > 160 mm Hg; and hypotension = systolic blood pressure < mm Hg. These boundaries also served as guidelines for the treatment of intraoperative hemodynamic abnormalities.

Patients were cared for in the postanesthesia care unit or the ICU until at least 8:00 AM of the morning after surgery. Clinical care was guided by the routine 12-lead ECG obtained immediately after surgery and others obtained by the physicians primarily caring for the patients. Analgesia was provided with morphine sulfate via patient-controlled analgesia with 1.5 mg available every 8 min in addition to a 1 mg/h continuous infusion. Heart rate and arterial blood pressure were recorded hourly in an ICU setting, and antihypertensive medications, fluid administration, and urinary output were measured until 8:00 AM on postoperative Day 1. Regardless of the choices of the clinicians caring for the patients, the study protocol required obtaining a standard 12-lead ECG immediately after surgery and on postoperative Days 1 and 2; serum creatinine on postoperative Days 1, 3, and 7; and creatine kinase-MB at 8:00 AM on postoperative Day 1. This strategy of cardiac surveillance was based on studies showing standard 12-lead ECG on the day of surgery and the first two postoperative days to be

the most sensitive strategy for diagnosing postoperative myocardial infarction (9), and that 85% of creatine kinase-MB increases after noncardiac surgery occur in the first 24 h (10).

Patients were visited daily in the hospital by a physician from the research team who was not involved in their clinical care but who assessed any postoperative complications. Such pulmonary complications included pneumonia (defined as new postoperative infiltrates on chest radiograph, a temperature > 38°C for at least 24 h, production of purulent sputum or cultures of pathogens, and antibiotic treatment received as part of therapy), reintubation, or prolonged intubation (> 24 h). Cardiovascular complications included myocardial infarction (defined as unequivocal new Q waves at least 0.04 s in duration, loss of R waves in the precordial leads signifying transmural infarction, or persistent ST-T wave abnormalities consistent with subendocardial infarction in the presence of a positive creatine phosphokinase-MB determination > 40 IU); myocardial ischemia (determined by transient ST-segment elevation >2 mm or downsloping depression >1 mm on standard 12-lead ECG in the absence of a positive creatine phosphokinase-MB determination), angina, cardiac arrest, or congestive heart failure (new or worsened with respiratory distress and rales on pulmonary examination or classic chest radiograph changes improving promptly with diuretic therapy). Peripheral vascular complications included the loss of a Doppler-detected pulse requiring the institution of anticoagulation or the need for vascular reoperation during the same hospital admission. Lastly, renal insufficiency was defined as an increase in serum creatinine on postoperative Day 0, 1, 3, or 7 to > 1.5 mg/dL accompanied by an increase > 0.8 mg/dL or the need for dialysis. We also recorded the number of hours patients spent in an ICU setting, days spent in the hospital, and in-hospital deaths.

Between 7:00 AM and 9:00 AM on postoperative Day 1, three blood samples were drawn from the arterial line at 30-min intervals for subsequent plasma catecholamine level determinations. Plasma norepinephrine and epinephrine levels were determined by high-performance liquid chromatography using solid state extraction with a detection limit of 5 pg/mL for norepinephrine and 6 pg/mL for epinephrine. The norepinephrine and epinephrine levels measured from the three different samples collected at different times were then averaged in an attempt to describe sympathetic tone, taking into account potentially rapid changes in plasma catecholamine concentrations (11). Blood from the last sample was used to measure plasma clonidine levels by radioimmune assay technique. The detection limit of the assay for clinical samples in heparinized plasma was 0.050 ng/mL (12). The coefficients of variation ranged from 10% to 13%.

The ELI-100 (Mortara Instruments, Milwaukee, WI) continuous 12-lead ECG monitor was applied to patients upon arrival in the operating room and removed at discharge to the floor or at 48 h postoperatively (whichever came first), unless technical difficulties or patient mobilization precluded further monitoring. The ECG monitor had a flat frequency response of 0–100 Hz. It acquired and analyzed the 12-lead ECG every 20 s and could store a maximum of 110 standard 12-lead ECGs (13). The monitor was programmed to save hourly ECG tracings and any ECG that showed a 2-mm deviation from the previous baseline in one lead, or a 1-mm deviation in two leads. We chose these thresholds to decrease motion artifacts. The same thresholds were used by Krucoff et al. (13) in monitoring patients after coronary thrombolysis. The incidence of perioperative myocardial ischemia was determined for patients without paced rhythms, left bundle-branch block, left ventricular hypertrophy with strain, or digitalis-induced ST-segment abnormalities. The ECGs were read by a cardiologist who was unaware of the clinical scenario. ECG ischemia was defined as 1 mm or more of ST-segment depression in any lead or a 2-mm ST-segment elevation from preoperative baseline lasting for >1 min.

The Wilcoxon rank sum test was used to analyze all continuous data except for postoperative vital signs and hospital charges. For these two variables, the Student's *t*-test was used with no correction for repeated measures. Categorical data were analyzed using the χ^2 test. However, when analyzing the incidence of myocardial ischemia during postoperative epochs, a simple binomial analysis was performed by considering those patients who had ischemic episodes in one epoch, but not another. $P \leq 0.05$ was considered significant. The study was originally designed to detect a reduction in incidence of postoperative myocardial ischemia from 33% in the placebo group to 15% with clonidine. This difference would require 80 patients per study group, and that quantity was set as the enrollment goal. The overall incidence of myocardial ischemia in the first 61 patients was approximately 28%, without a difference between the two groups. This observation, coupled with low blood levels of clonidine in treated patients, made it unlikely that outcome differences could be determined in the study we designed. This led to our decision to terminate the study and report our early experience. Consequently, the results we present below are based on sample sizes that have low power for detecting differences in overall outcome.

Results

Patient demographic information is presented in Table 1. The median age of patients was 68 yr, and 82% of

Table 1. Patient Demographics

	Placebo (n = 31)	Clonidine (n = 30)	P value
Age (yr)[a]	68.00 (63.00, 75.00)	68.50 (61.75, 74.25)	0.73
Sex (male/female)	16/15	13/17	0.52
Race (white/black)	20/11	12/18	0.06
Operation (aortic/femoral/orthopedic/other)	15/10/3/3	17/9/3/1	0.76
Hypertension	21 (67.7%)	17 (56.7%)	0.37
Diabetes mellitus	8 (25.8%)	10 (33.3%)	0.52
Angina	3 (9.7%)	7 (23.3%)	0.15
Congestive heart failure	5 (16.1%)	2 (6.7%)	0.25
Previous myocardial infarction	5 (16.1%)	9 (30%)	0.20
Previous coronary revascularization	6 (19.4%)	6 (20%)	0.95
Preoperative hematocrit (%)[a]	37.4 (34.0, 41.4)	37.6 (34.1, 40.9)	0.98
Preoperative creatinine (mg/dl)[a]	1.20 (1.00, 1.70)	1.15 (0.90, 1.32)	0.41
Preoperative β-adrenergic receptor blocking drugs	6 (19.4%)	1 (3.3%)	0.05
Preoperative slow calcium channel blocking drugs	12 (38.7%)	10 (33.3%)	0.66
Preoperative nitroglycerin	6 (19.4%)	3 (10%)	0.30
Preoperative ACE inhibitors	7 (22.6%)	7 (23.3%)	0.94
Smoking (never/current/past)	5/13/13	6/16/8	0.45

ACE = angiotensin-converting enzyme.
[a] Median (interquartile range).

these patients underwent vascular surgical procedures. More patients in the placebo group were taking β-adrenergic receptor blocking drugs before surgery (P = 0.05). There was a trend toward a larger number of black patients in the clonidine group (P = 0.06).

We found no difference in the amount of sufentanil or thiamylal needed to induce and maintain anesthesia between the two groups of patients. In 49 (25 placebo, 24 clonidine) patients, we averaged the end-tidal concentrations of enflurane measured at 1-min intervals during surgery. Median intraoperative inspired enflurane concentrations were lower by 25% (P = 0.05) in the clonidine group. The length of operation and time to extubation did not differ between the two groups. There were no differences between the two groups in the percentage of patients who required ephedrine, phenylephrine, atropine, or β-adrenergic receptor blocking drugs during surgery. Estimated blood loss, intraoperative urine output, IV crystalloid infusion, and the use of red blood cell transfusions were not different between the two groups. Patients in the clonidine group were less likely to receive colloids (P = 0.05). Clonidine reduced the incidence of tachycardic episodes (heart rate > 100 bpm for ≥ 5 min) during surgery (2/24 vs 9/26 in the placebo group; (P = 0.03) but did not affect the incidence of other hemodynamic abnormalities. The transdermal system was removed before 72 h after application in five patients due to hypotension (three in the placebo group and two in the clonidine group).

Patients who received clonidine had median plasma drug levels of 0.75 ng/mL (interquartile range = 0.625, 1.095 ng/mL) during the morning after surgery which resulted in significantly lower plasma norepinephrine and epinephrine levels (Table 2). Despite this, they were no less likely to receive labetolol, nitroglycerin, nitroprusside, or nifedipine in the postoperative period for postoperative hypertension than were control patients. During the period from the end of surgery until 8:00 AM of postoperative Day 1 (median 18 h after surgery), clonidine patients were neither more likely to receive colloid or extra fluid infusions ("boluses") nor to receive more crystalloid than did patients in the placebo group (Table 2). The dose of IV morphine received by patient-controlled anesthesia was not different between the patients in the two groups (Table 2).

Heart rates were significantly slower in clonidine patients for only the first, second, third, and fifth postoperative hours, whereas the mean arterial pressure was significantly lower in clonidine patients at 14, 15, and 16 h after surgery. Postoperative heart rate data is presented in Figure 1. Because there were more patients receiving chronic β-adrenergic antagonist drugs in the placebo group, we also compared postoperative heart rates in those patients not taking such drugs. The results were very similar, with statistically significant differences in heart rate seen only at 1, 2, 4, and 5 h after surgery (lower in clonidine group).

In patients with continuous ECG in which ischemic changes could be read, the incidence of intraoperative myocardial ischemia was diminished in the patients who received clonidine (1/28) compared to the placebo group (5/24, P = 0.05; see Table 3). Evaluation of the patients not receiving chronic β-adrenergic blocking drugs revealed that intraoperative myocardial ischemia still occurred less frequently (1/27) in the clonidine group than in the placebo group (5/18; P = 0.02). Indeed, intraoperative ischemia did not occur in

Table 2. Early Postoperative Data[a]

	Placebo (n = 31)	Clonidine (n = 30)	*P* value
Norepinephrine (pg/mL)[b,c]	709 (400, 1236)	424 (236, 809)	0.03
Epinephrine (pg/mL)[b,c]	122.2 (74.2, 215.7)	85.8 (35.8, 121.2)	0.01
Labetolol (*n*)	4 (12.9%)	4 (13.3%)	0.96
NTG and/or SNP (*n*)	6 (19.4%)	7 (23.3%)	0.70
Nifedipine (*n*)	4 (12.9%)	7 (23.3%)	0.29
Fluid bolus (*n*)	18 (58.1%)	16 (53.3%)	0.71
Colloid (*n*)	6 (19.4%)	7 (23.3%)	0.70
Crystalloid (mL/h)[b]	131 (108.5, 160.8)	120 (90.0, 149.5)	0.26
Morphine (mg/h)[b]	1.582 (0.736, 2.115)	1.514 (0.698, 2.359)	0.86
Urine (mL/h)[b]	96.8 (65.0, 154.0)	70.5 (59.4, 115.9)	0.05

NTG = nitroglycerin; SNP = sodium nitroprusside.
[a] From the end of surgery until 8:00 AM of postoperative Day 1 (median 18 h after surgery).
[b] Median (interquartile range).
[c] Epinephrine and norepinephrine levels obtained between 7:00 AM and 9:00 AM on postoperative Day 1.

any patient receiving β-adrenergic blocking drugs before surgery. The incidence of postoperative myocardial ischemia was not different between patients receiving clonidine or placebo (Table 3); this result did not change when patients taking β-adrenergic blocking drugs were excluded from the analysis.

When the postoperative period was divided into three epochs (first, 1–5 h; second, 6–10 h; and third, 11–15 h), we found that the heart rate increased significantly from each epoch to the next (for example $P = 0.00003$ for the first versus the second epoch). There was also a trend toward higher postoperative heart rates in the second and third epochs for patients who experienced any episodes of postoperative myocardial ischemia. Six patients experienced myocardial ischemia during the first epoch and one during the third epoch, but this difference was not significant ($P = 0.12$ by simple binomial analysis).

Patients who received clonidine had lower hourly urinary output after surgery than patients in the control group (Table 2). However, this difference did not appear to be clinically relevant, as serum creatinine levels measured before surgery and on postoperative Days 1, 3, and 7 were not significantly different between the two groups. One patient assigned to the placebo group, who underwent esophagogastrectomy, died 23 days after surgery from adult respiratory distress syndrome. We found no significant differences in the occurrence of major complications, the length of ICU stay, or the length or cost of hospitalization between the two groups (Table 4).

Discussion

We chose to combine transdermal and oral clonidine to provide perioperative sympatholysis because IV clonidine is not routinely available in the United States and because oral clonidine has a half-life of 8–16 h, which we did not believe to be long enough to provide effective sympatholysis in the postoperative period. Using a combined oral-transdermal regimen of clonidine (two oral doses of 3 μg/kg and 0.2 mg/day transdermal), Segal et al. (14) provided patients with stable mean plasma levels of clonidine levels of 1.5 ng/mL for at least 60 h. The doses of clonidine we used in our study were less and were insufficient to prevent increases in heart rate beyond the first 5 h after surgery (Figure 1).

Pretreatment with α_2 agonists may help to prevent the sympathetic nervous system from mediating the cascade of sensitization and hyperalgesia that can worsen postoperative pain. However, unlike others (14,15), we did not find significant differences between treatment and control groups in the amount of morphine used after surgery. This may have been due to our lower clonidine levels and age-related differences in α_2 receptor density and function. Perhaps patients in the clonidine group had superior analgesia, despite consuming similar amounts of morphine, but since we did not measure pain scores we can only speculate on this last point.

The hyperadrenergic response to surgery may contribute to the high incidence of myocardial ischemia due to tachycardia and increased afterload which increase myocardial oxygen demand. Catecholamine-induced coronary vasospasm and platelet aggregation may also decrease myocardial oxygen supply. α_2-Adrenergic agonists mediate a reduction in norepinephrine release which may benefit surgical patients with CAD by increasing coronary blood flow (16) and reducing blood pressure and end-systolic wall stress,

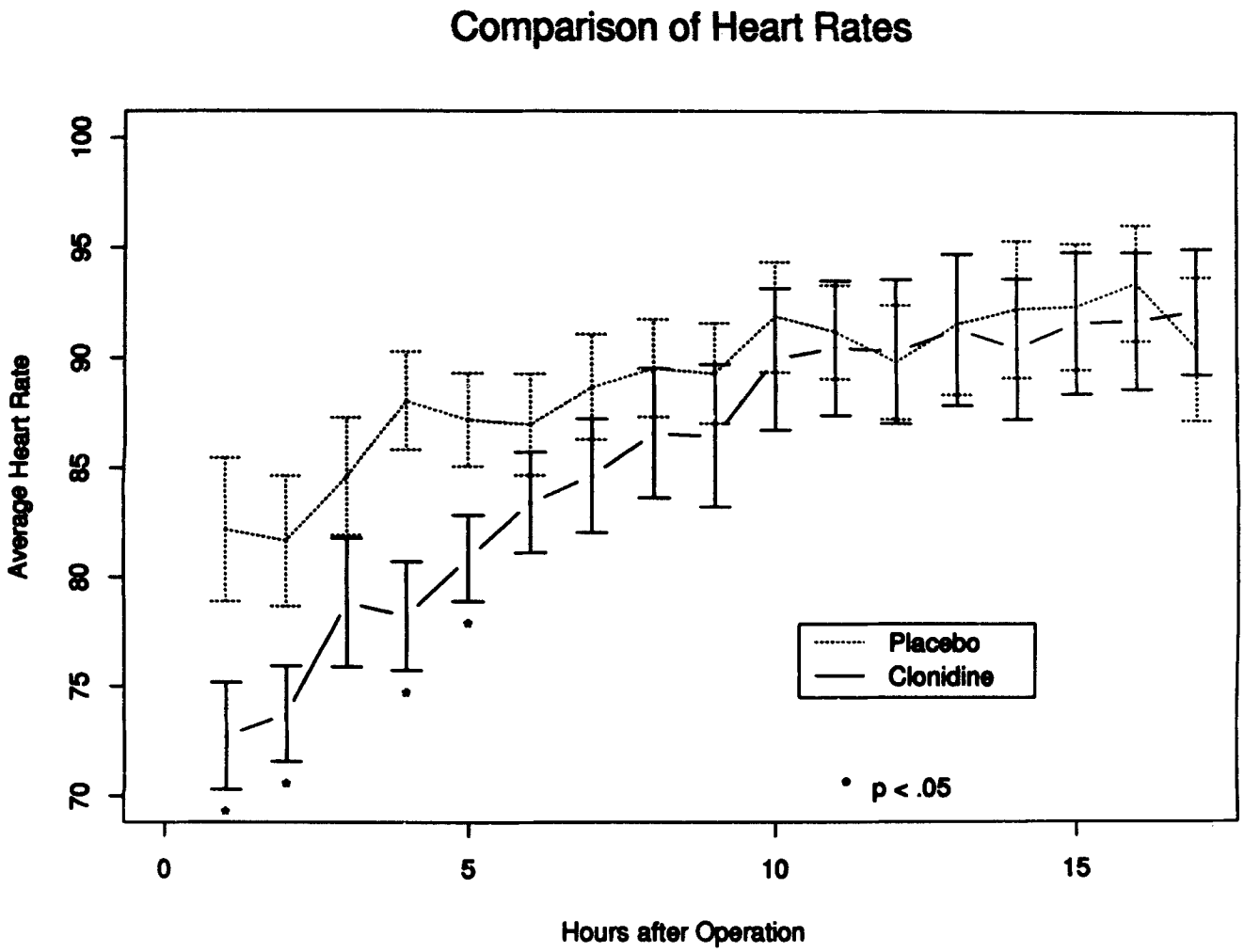

Figure 1. Clonidine results in lower heart rates in patients in an intensive care unit setting at 1, 2, 4, and 5 h after noncardiac surgery. The verticle axis represents heart rate in beats per minute (mean ± SEM). The horizontal axis represents time in hours after the end of surgery.

Table 3. Perioperative Myocardial Ischemia

	Placebo	Clonidine	*P* value
Hours of postoperative 12-lead ECG monitoring[a]	17.0 (13.0, 21.5)	18.0 (15.0, 31.5)	0.29
Intraoperative myocardial ischemia	5/24 (20.8%)	1/28 (3.6%)	0.05
Postoperative myocardial ischemia	5/26 (19.2%)	6/28 (21.4%)	0.84
Perioperative myocardial ischemia	8/26 (30.8%)	7/28 (25.0%)	0.63

ECG = electrocardiogram.
[a] Median (interquartile range).

and preserving left ventricular function (17). High doses of IV clonidine (7 μg/kg) significantly attenuate the endocrine surge and increased metabolic rate in the first 5 h after aortic surgery (18). In one study, premedication with clonidine 0.2 mg *per os* decreased prebypass myocardial ischemia during coronary artery bypass grafting (19), whereas in another study, clonidine 4 μg/kg was ineffective in preventing myocardial ischemia in patients undergoing carotid artery surgery (20). The low dose of clonidine that we used decreased the incidence of intraoperative but not postoperative myocardial ischemia. Thus, we believe that higher doses of clonidine may be more effective in blunting postoperative tachycardia and myocardial ischemia. However, the use of larger doses of α_2 agonists may reduce coronary perfusion pressure after general surgery (21) and increase the need for inotropic support after cardiac surgery (22).

Continuous ECG devices can detect "silent" myocardial ischemia after percutaneous transluminal

Table 4. In-Hospital Complications and Outcomes

	Placebo (n = 31)	Clonidine (n = 30)	P value
Total cardiac	6 (19.4%)	5 (16.7%)	0.78
Myocardial infarction (7th POD)	2 (6.5%)	0	0.16
Congestive heart failure	5 (16.1%)	4 (13.3%)	0.76
Clinically evident myocardial ischemia	2 (6.5%)	1 (3.3%)	0.57
Cardiac arrest	1 (3.2%)	0	0.32
Total pulmonary	3 (9.7%)	3 (10.0%)	0.96
Postoperative ventilation >24 h	3 (9.7%)	0	0.08
Pneumonia	2 (6.5%)	3 (10.0%)	0.61
Reintubation	2 (6.5%)	0	0.16
Peripheral vascular	4/26 (15.4%)	3/26 (11.5%)	0.69
Postoperative anticoagulation	2/26 (7.7%)	3/26 (11.5%)	0.64
Reoperation for thrombosis	2/26 (7.7%)	2/26 (7.7%)	1.00
Renal insufficiency	0	1 (3.3%)	0.31
>1 complication	11 (35.5%)	11 (36.7%)	0.92
Deaths (7 days)	0	0	N/A
Hours ICU care[a]	22 (17, 50)	21 (16, 43)	0.72
Days hospitalized after surgery[a]	8.0 (7.0, 12.0)	8.0 (6.7, 11.2)	0.95
Hospital costs[b]	22,491 ± 3086	17,230 ± 1401	0.13

POD = postoperative day; ICU = intensive care unit.
[a] Median (interquartile range).
[b] Mean (±SEM).

coronary angioplasty or thrombolysis (13). Although these devices detect intraoperative myocardial ischemia less frequently than do Holter devices in the same patients (14% vs 26%), their specificity for predicting adverse cardiac events is high (23). Our threshold (2 mm = 0.2 mV ST segment change in one lead) for storing additional ECGs beyond the hourly tracings may have lowered the sensitivity of ECG in detecting myocardial ischemia. However, by avoiding artifactual storage of complexes, we were able to monitor patients for 17.5 h (median) postoperatively without exceeding the system storage limit of approximately 100 ECGs. It also would have been impractical to monitor patients for longer periods once they ambulate.

Various strategies have been proposed to reduce cardiac morbidity during and after vascular surgery including the prophylactic use of antianginal drugs, and special anesthetic techniques. However, IV infusions of potent vasoactive drugs require intensive nursing care and high-dose narcotic anesthesia usually necessitates postoperative ventilation with its attendant risks and costs. Epidural narcotics reduce postoperative hypertension, tachycardia, and norepinephrine levels after vascular surgery (5). Still, concerns about expense, respiratory depression, and neuroaxis hematoma have limited the use of peridural techniques in many patients.

The dose of clonidine used in this study (0.3 mg *per os* before surgery and a transdermal system that released 0.2 mg/day) decreased plasma catecholamine levels on the first postoperative day, and reduced intraoperative myocardial ischemia. We believe that further clinical trials should be undertaken in larger groups of patients and with larger doses of oral and transdermal clonidine, with the goal of suppressing the usual increase in postoperative heart rate. Such trials would test the hypothesis that sympatholytic therapy with clonidine can reduce postoperative tachycardia and myocardial ischemia, and possibly improve functional outcome and reduce costs after noncardiac surgery in high-risk patients.

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